REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

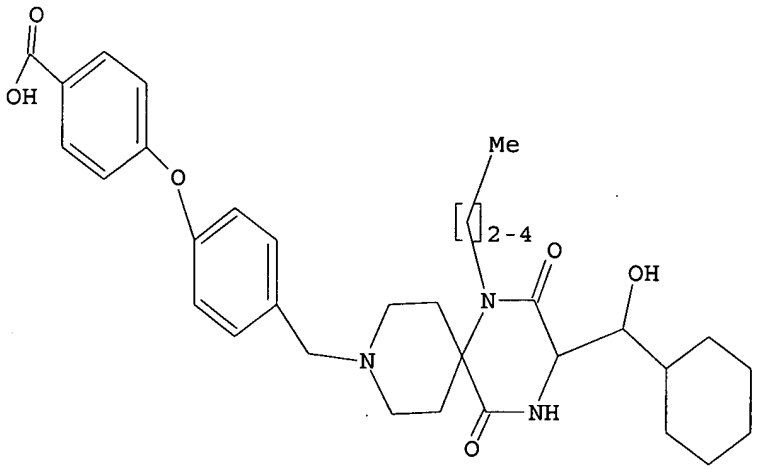
=> d his

(FILE 'HOME' ENTERED AT 13:38:54 ON 30 OCT 2006)

FILE 'REGISTRY' ENTERED AT 13:39:14 ON 30 OCT 2006
L1 STRUCTURE UPLOADED
L2 6 S L1
L3 57 S L1 FULL

FILE 'CAPLUS' ENTERED AT 13:40:56 ON 30 OCT 2006
L4 38 S L3

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=>

STN- Structure Search 10/30/06

10/527,193

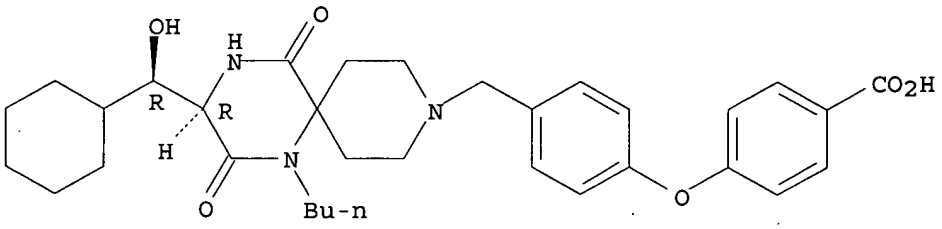
=> d ibib abs hitstr 1-38

L4 ANSWER 1 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:769177 CAPLUS
DOCUMENT NUMBER: 145:180928
TITLE: Human neutrophil α-defensin 4 inhibition of HIV-1
INVENTOR(S): Lu, Wuyuan; Cocchi, Fiorenza; Wu, Zhibin
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 7pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006172945	A1	20060803	US 2006-347538	20060203
PRIORITY APPLN. INFO.:			US 2005-649873P P	20050203

AB A method to reduce replication of HIV-1, involving administering a therapeutically effective amount of recombinant HNP4 to a subject in need thereof to combat HIV-1 infection. The HNP4 agent may be utilized in pharmaceutical compns. including a pharmaceutically acceptable carrier and an anti-viral agent, e.g., an anti-viral agent, or combination of such agents, such as nucleoside RT inhibitors, CCR5 inhibitors/antagonists, viral entry inhibitors, and functional analogs thereof.
IT 461443-59-4, AK602
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(human neutrophil α-defensin 4 inhibition of HIV-1)
RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:676597 CAPLUS
DOCUMENT NUMBER: 145:117362
TITLE: Compositions for down-regulation of CCR5 expression and methods of use thereof
INVENTOR(S): Redfield, Robert R.; Amoroso, Anthony; Davis, Charles E.; Heredia, Alonso
PATENT ASSIGNEE(S): University of Maryland Biotechnology Institute, USA
SOURCE: U.S. Pat. Appl. Publ., 35 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006154857	A1	20060713	US 2005-281195	20051116
WO 2005001027	A2	20050106	WO 2004-US15681	20040517
WO 2005001027	A3	20060126		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-471453P P 20030516
WO 2004-US15681 A2 20040517

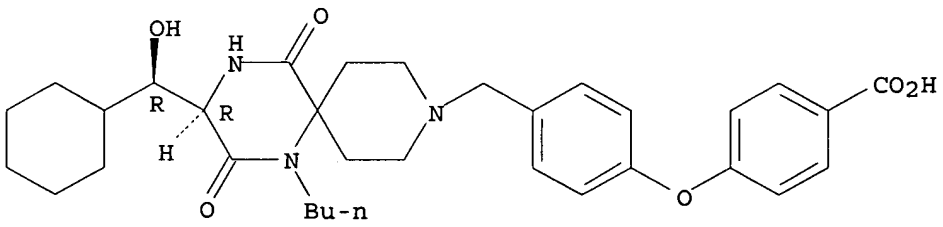
AB The present invention relates to the downregulation of surface receptor CCR5 expression through manipulation of the cell cycle in activated lymphocytes by administering a composition that arrests the G1 phase of the cell cycle, thereby reducing receptor sites for entry of HIV into T cells, and thus, the effects of HIV. Further, compns. are disclosed that include at least one G1 phase arresting agent and at least one antiviral agent, wherein the combination of agents synergistically enhances the activity of the antiviral agent.

IT 461443-59-4, AK602
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for down-regulation of CCR5 expression by arresting G1 phase of cell cycle of activated lymphocytes and decreasing HIV virus entry and combination with other antiviral agents)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 3 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:578211 CAPLUS
DOCUMENT NUMBER: 145:62897
TITLE: Preparation of spirotropane compounds and therapeutic use as modulators of chemokine receptor activity
INVENTOR(S): Chan Chun Kong, Laval; Moinet, Christophe; Courchesne, Marc; Vaillancourt, Louis; Blais, Charles; Bubenik, Monica
PATENT ASSIGNEE(S): Virochem Pharma Inc., Can.
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

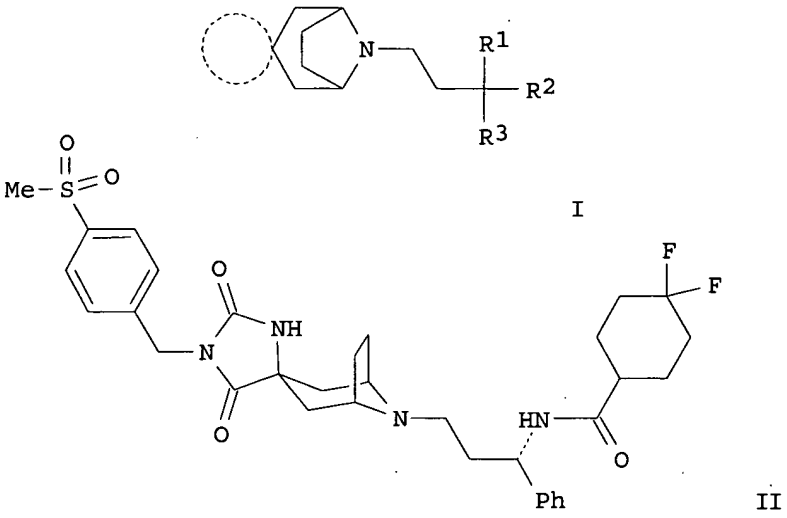
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006060919	A1	20060615	WO 2005-CA1878	20051209

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-634266P P 20041209
US 2005-693051P P 20050623

OTHER SOURCE(S): MARPAT 145:62897
GI



I II

AB Spiro compds. according to formula (I) are claimed: wherein R1 = NR7R9; R2 = (un)substituted C1-10 alkyl, C2-10 alkenyl, 3-10 membered heterocycle, etc.; R3 = H, (un)substituted C1-10 alkyl or C6-12 aryl; R7 = H, (un)substituted C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl; R9 = H or (un)substituted C1-10-alkyl; and ring A represents a 5 or 6 membered heteroring substituted once or twice with a keto substituent. These compds. and their pharmaceutical acceptable salts are used in combinations or in pharmaceutical compns. and are useful in the modulation of CCR5 chemokine receptor activity (no data given). I are useful in the prevention or treatment of certain inflammatory diseases, immunoregulatory diseases, organ transplantation reactions and in the prevention and treatment of infectious diseases such as HIV infections. Preparation of I is exemplified. For example, II was prepared from 4,4-difluorocyclohexanecarboxylic acid ((S)-3-oxo-1-phenylpropyl)amide and 3-(4-methanesulfonylbenzyl)bicyclo[3.2.1]-1α,3,8-

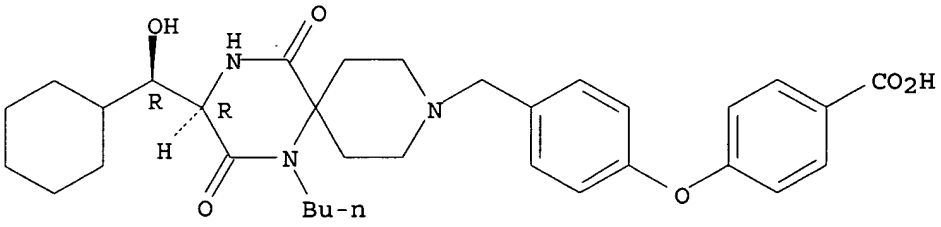
triazaspiro[4.5]dodecan-2,4-dione hydrochloride (preparation given).

IT 461443-59-4, GW873140
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(addnl. therapeutic agent; preparation of spirotropane compds. and therapeutic use as modulators of chemokine receptor activity)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

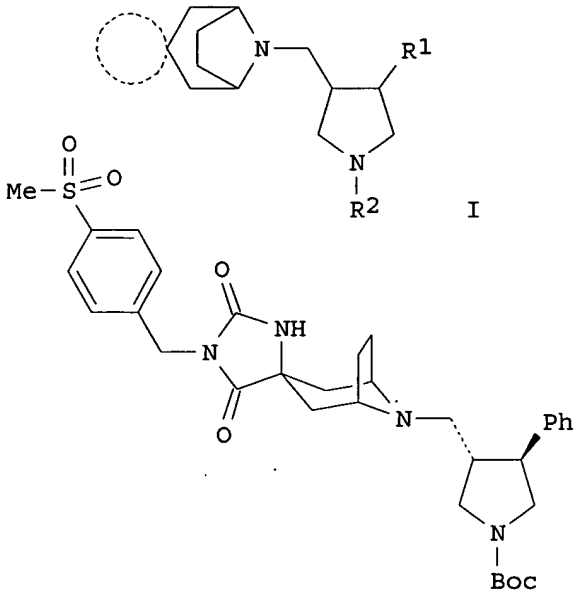
ACCESSION NUMBER: 2006:558325 CAPLUS
DOCUMENT NUMBER: 145:62894
TITLE: Preparation of spirotropane compounds and methods for the modulation of chemokine receptor activity to block cellular entry of HIV
INVENTOR(S): Chan Chun Kong, Laval; Moinet, Christophe; Courchesne, Marc; Vaillancourt, Louis; Bubenik, Monica
PATENT ASSIGNEE(S): Virochem Pharma Inc., Can.
SOURCE: PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006060918	A1	20060615	WO 2005-CA1877	20051209

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-634257P P 20041209
OTHER SOURCE(S): MARPAT 145:62894
GI



I

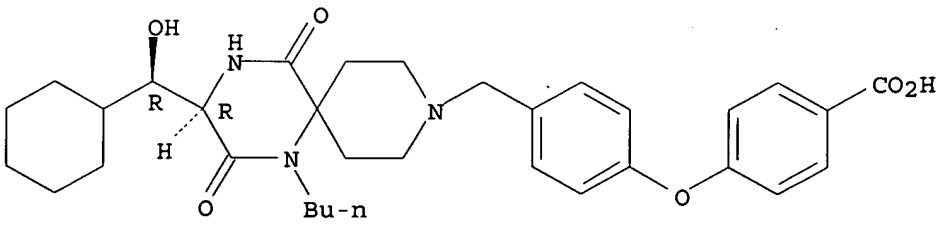
AB Compds. according to formula I (wherein the R1= (un)substituted alkyl, alkenyl, etc.; R2 = H, cycloalkylcarbonyl, ester, etc.; and A = a 5 or 6 membered heteroring involving a nitrogen or oxygen atom and one or two keto substituent) are claimed. These compds. and their pharmaceutical acceptable salt are used in combinations or pharmaceutical compns. and are useful in modulation of CCR5 chemokine receptor activity and blocking cellular entry of HIV (no biol. data given). Preparation of I is exemplified. For example, II was prepared from 3-(4-methanesulfonylbenzyl)bicyclo[3.2.1]-1a,3,8-triazaspiro[4.5]dodecan-2,4-dione hydrochloride (preparation given) and (3R,4S)-3-formyl-4-phenylpyrrolidine-1-carboxylic acid tert-Bu ester (preparation given).

IT 461443-59-4, GW873140
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(addnl. therapeutic agent; preparation of spirotropane compds. and methods for modulation of chemokine receptor activity to block cellular entry of HIV)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:542321 CAPLUS
DOCUMENT NUMBER: 144:481019
TITLE: Method for treating HIV infection through co-administration of tipranavir and GW873140
INVENTOR(S): Kraft, Michael Friedrich; Mayers, Douglas Lytle
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany
SOURCE: PCT Int. Appl., 11 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006060177	A1	20060608	WO 2005-US41757	20051117
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2006160859	A1	20060720	US 2005-281020	20051117
PRIORITY APPLN. INFO.:			US 2004-632565P	P 20041201

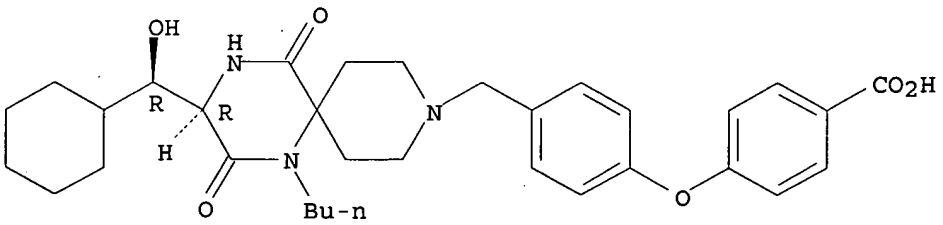
AB Method is disclosed for treating HIV infection through co-administration of tipranavir and GW873140.

IT 461443-59-4, GW 873140
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for treating HIV infection by co-administration of tipranavir and GW873140)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

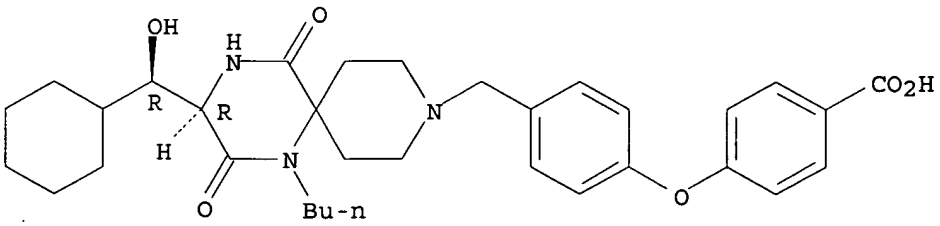


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:479520 CAPLUS
DOCUMENT NUMBER: 145:327740
TITLE: Evaluation of the drug interaction potential of aplaviroc, a novel human immunodeficiency virus entry inhibitor, using a modified Cooperstown 5 + 1 cocktail

AUTHOR(S): Johnson, Brendan M.; Song, Ivy H.; Adkinson, Kimberly K.; Borland, Julie; Fang, Lei; Lou, Yu; Berrey, M. Michelle; Nafziger, Anne M.; Piscitelli, Stephen C.; Bertino, Joseph S., Jr.
CORPORATE SOURCE: GlaxoSmithKline, Research Triangle Park, NC, USA
SOURCE: Journal of Clinical Pharmacology (2006), 46(5), 577-587
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aplaviroc is a novel CCR5 antagonist, a class of compds. under investigation as viral entry inhibitors for the treatment of human immunodeficiency virus infection. A modified Cooperstown 5+1 cocktail was used to assess the drug interaction potential of aplaviroc. Fifteen healthy subjects were administered single oral doses of caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and midazolam (CYP3A) alone (reference treatment) and during steady-state administration of aplaviroc (400 mg every 12 h, test treatment). Metabolite-to-parent area under the plasma concentration vs. time curve (AUC) ratios (paraxanthine/caffeine and 5-hydroxyomeprazole/omeprazole), oral clearance (S-warfarin), AUC (midazolam), and metabolite-to-parent urinary excretion ratio (dextrorphan/dextromethorphan) were determined The test-to-reference treatment ratios (geometric mean ratio and 90% confidence interval) were caffeine, 1.06 (0.97-1.17); S-warfarin, 0.93 (0.76-1.15); omeprazole, 1.07 (0.98-1.16); dextromethorphan, 1.17 (0.97-1.42); midazolam, 1.30 (1.04-1.63). No significant inhibition of CYP1A2, CYP2C9, CYP2C19, or CYP2D6 enzyme activity was observed Mild inhibition of CYP3A isoenzymes should not preclude the use of concomitant CYP3A substrates in future clin. studies with aplaviroc.
IT 461443-59-4, Aplaviroc
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aplaviroc was well tolerated in healthy subjects, did not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 enzyme activity, while inhibition of CYP3A isoenzymes was mild evident)
RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

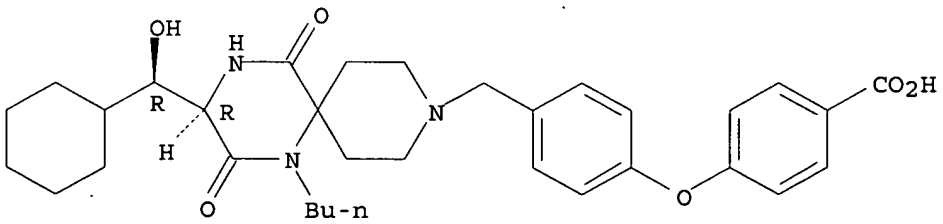


REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:396751 CAPLUS
DOCUMENT NUMBER: 144:466332
TITLE: Structural and Molecular Interactions of CCR5 Inhibitors with CCR5
AUTHOR(S): Maeda, Kenji; Das, Debananda; Ogata-Aoki, Hiromi; Nakata, Hirotomo; Miyakawa, Toshikazu; Tojo, Yasushi;

Norman, Rachael; Takaoka, Yoshikazu; Ding, Jianping; Arnold, Gail F.; Arnold, Eddy; Mitsuya, Hiroaki
CORPORATE SOURCE: Department of Hematology and Department of Infectious Diseases, Kumamoto University Graduate School of Medical and Pharmaceutical Sciences, Kumamoto, 860-8556, Japan
SOURCE: Journal of Biological Chemistry (2006), 281(18), 12688-12698
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have characterized the structural and mol. interactions of CC-chemokine receptor 5 (CCR5) with three CCR5 inhibitors active against R5 human immunodeficiency virus type 1 (HIV-1) including the potent in vitro and in vivo CCR5 inhibitor aplaviroc (AVC). The data obtained with saturation binding assays and structural analyses delineated the key interactions responsible for the binding of CCR5 inhibitors with CCR5 and illustrated that their binding site is located in a predominantly lipophilic pocket in the interface of extracellular loops and within the upper transmembrane (TM) domain of CCR5. Mutations in the CCR5 binding sites of AVC decreased gp120 binding to CCR5 and the susceptibility to HIV-1 infection, although mutations in TM4 and TM5 that also decreased gp120 binding and HIV-1 infectivity had less effects on the binding of CC-chemokines, suggesting that CCR5 inhibition targeting appropriate regions might render the inhibition highly HIV-1-specific while preserving the CC chemokine-CCR5 interactions. The present data delineating residue by residue interactions of CCR5 with CCR5 inhibitors should not only help design more potent and more HIV-1-specific CCR5 inhibitors, but also give new insights into the dynamics of CC-chemokine-CCR5 interactions and the mechanisms of CCR5 involvement in the process of cellular entry of HIV-1.
IT 461443-59-4, Aplaviroc
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structural and mol. interactions of CCR5 inhibitors with CCR5)
RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

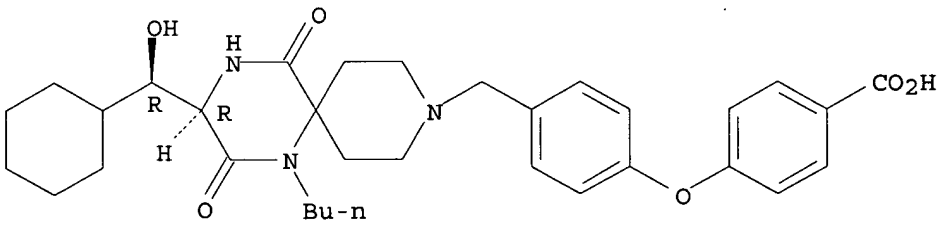


REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:254138 CAPLUS
DOCUMENT NUMBER: 145:201842
TITLE: Development of a novel dual CCR5-dependent and CXCR4-dependent cell-cell fusion assay system with inducible gp160 expression
AUTHOR(S): Ji, Changhua; Zhang, Jun; Cammack, Nick; Sankuratri,

Surya
CORPORATE SOURCE: Viral Diseases, Roche Palo Alto, Palo Alto, CA, USA
SOURCE: Journal of Biomolecular Screening (2006), 11(1), 65-74
CODEN: JBISF3; ISSN: 1087-0571
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the current study, a novel coreceptor-specific cell-cell fusion (CCF) assay system is reported. The system possesses the following features: dual CCR5-dependent and CXCR4-dependent CCF assays, all stable cell lines, inducible expression of gp160 to minimize cytotoxicity, robust luciferase reporter, and 384-well format. These assays have been validated using various known HIV entry inhibitors targeting various stages of the HIV entry/fusion process, including fusion inhibitors, gp120 inhibitors, CCR5 antagonists, CCR5 antibodies, and CXCR4 antagonists. IC50 data generated from this assay system were well correlated to that from the antiviral assays. The effects of DMSO on this assay system were assessed, and a 2- to 3-fold increase in luciferase activity was observed in the presence of 0.05% to 2% DMSO. Although cell-cell fusion efficiency was enhanced, no changes in drug response kinetics for entry inhibitors were found in the presence of 0.1% or 0.5% DMSO. This assay system has been successfully used for the identification and characterization of thousands of CCR5 inhibitors.
IT 461443-59-4, GW873140
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GW873140 inhibited CCR5-dependent cell-cell fusion assays in HeLa-R5 and HeLa-X4 cell lines)
RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:117207 CAPLUS
DOCUMENT NUMBER: 144:213021
TITLE: Preparation of pseudopeptide phosphate prodrugs of HIV protease inhibitors
INVENTOR(S): Degoey, David A.; Flosi, William J.; Grampovnik, David J.; Klein, Larry L.; Kempf, Dale J.; Wang, Xiu C.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2006014282	A2	20060209	WO 2005-US23047 20050629
WO 2006014282	A3	20060511	

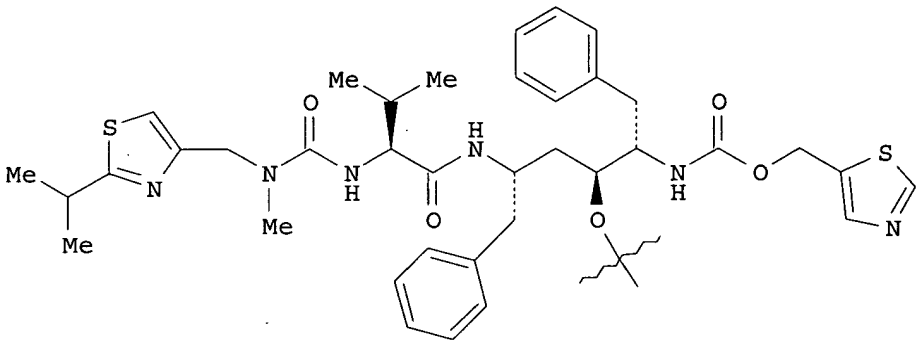
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-585710P P 20040706

OTHER SOURCE(S): CASREACT 144:213021; MARPAT 144:213021

GI



I

AB The invention discloses compds. A-L1-L2-OPO3H2 (L1 is a bond, CO or CO2; L2 is (CR1R2)1-5, where R1, R2 are H or alkyl; A is a pseudopeptide moiety, e.g., I, attached through its oxygen atom), as well as their alkyl or arylalkyl esters, metal or quaternary ammonium salts, for use as prodrugs of HIV protease inhibitors. Thus, disodium N1-[(1S,3S,4S)-1-benzyl-5-phenyl-3-[(phosphonatooxy)methoxy]-4-[[(1,3-thiazol-5-ylmethoxy)carbonyl]amino]pentyl]-N2-[[[(2-isopropyl-1,3-thiazol-4-yl)methyl](methyl)amino]carbonyl]-L-valinamide was prepared from the alc. (I-H) by treatment with Me sulfide and benzoyl peroxide in acetonitrile to form the 3-[(methylthio)methoxy] derivative, which was treated with phosphoric acid, mol. sieves and N-iodosuccinimide in THF and then with Na2S2O3 and Na2CO3.

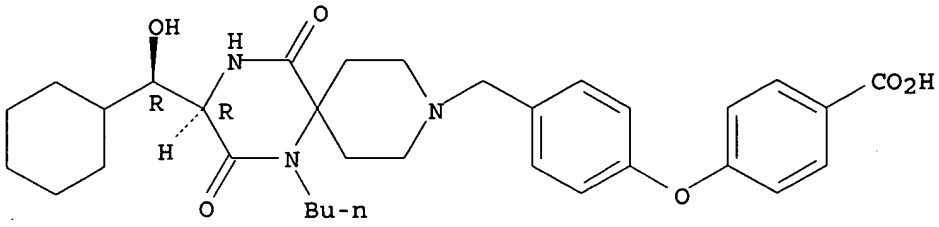
IT 461443-59-4, GW873140

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of pseudopeptide phosphate prodrugs of HIV protease inhibitors)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



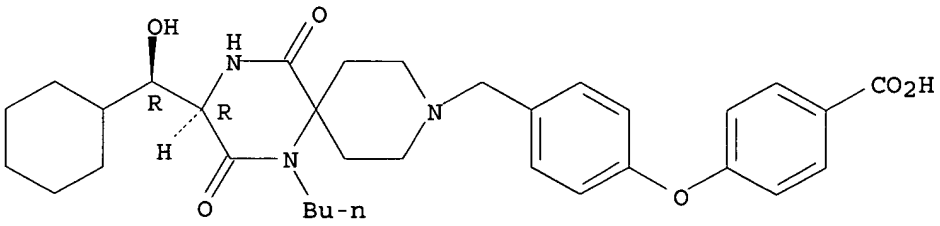
L4 ANSWER 10 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1256967 CAPLUS
DOCUMENT NUMBER: 144:368023
TITLE: CCR5: a target for therapeutic intervention of HIV-1 infection
AUTHOR(S): Mitsuya, Hiroaki
CORPORATE SOURCE: Dep. of Infectious Diseases, Dep. of Hematology, School of Medicine, Kumamoto University, Japan
SOURCE: Jikken Igaku (2005), 23(17), 2726-2731
CODEN: JIIGEF; ISSN: 0288-5514
PUBLISHER: Yodosha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review on human immunodeficiency virus-1 (HIV-1) invasion inhibitors and chemokine receptor antagonists, discussing (1) gp41 targeted inhibitors T-20 and T-1249 and CD4 binding inhibitors PRO542 and TNX-355 and anti-CXCR4 agents, (2) CCR5 antagonists maraviroc, aplaviroc, vicraviroc and TAK-652 and (3) structural anal. of CCR5 and CCR5 antagonist binding.

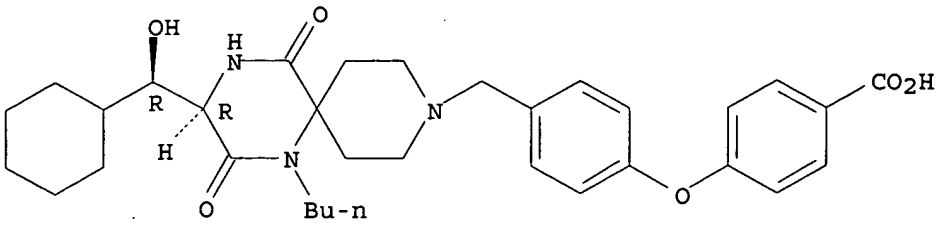
IT 461443-59-4, AK602
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CCR5 as a target for therapeutic intervention of HIV-1 infection)

RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 11 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1131007 CAPLUS
DOCUMENT NUMBER: 144:141709
TITLE: Emerging drug targets for antiretroviral therapy
AUTHOR(S): Reeves, Jacqueline D.; Piefer, Andrew J.
CORPORATE SOURCE: Department of Microbiology, University of Pennsylvania, Philadelphia, PA, USA
SOURCE: Drugs (2005), 65(13), 1747-1766
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review



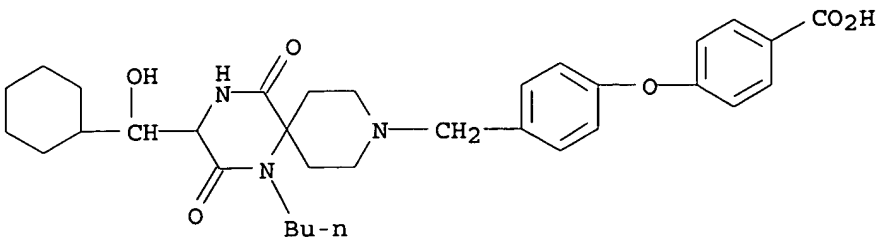
REFERENCE COUNT: 222 THERE ARE 222 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1016895 CAPLUS
DOCUMENT NUMBER: 143:415586
TITLE: G-Protein-Coupled Receptor Affinity Prediction Based on the Use of a Profiling Dataset: QSAR Design, Synthesis, and Experimental Validation
AUTHOR(S): Rolland, Catherine; Gozalbes, Rafael; Nicolaie, Eric; Paugam, Marie-France; Coussy, Laurent; Barbosa, Frederique; Horvath, Dragos; Revah, Frederic
CORPORATE SOURCE: Cerep, Rueil-Malmaison, 92500, Fr.
SOURCE: Journal of Medicinal Chemistry (2005), 48(21), 6563-6574
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A QSAR model accounting for "average" G-protein-coupled receptor (GPCR) binding was built from a large set of exptl. standardized binding data (1939 compds. systematically tested over 40 different GPCRs) and applied to the design of a library of "GPCR-predicted" compds. Three hundred and sixty of these compds. were randomly selected and tested in 21 GPCR binding assays. Positives were defined by their ability to inhibit by more than 70% the binding of reference compds. at 10 μM. A 5.5-fold enrichment in positives was observed when comparing the "GPCR-predicted" compds. with 600 randomly selected compds. predicted as "non-GPCR" from a general collection. The model was efficient in predicting strongest binders, since enrichment was greater for higher cutoffs. Significant enrichment was also observed for peptidic GPCRs and receptors not included to develop the QSAR model, suggesting the usefulness of the model to design ligands binding with newly identified GPCRs, including orphan ones.

IT 868056-95-5
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR design, synthesis, and exptl. validation of G-protein-coupled receptor affinity prediction based on use of a profiling dataset)

RN 868056-95-5 CAPLUS
CN Benzoic acid, 4-[4-[[1-butyl-3-(cyclohexylhydroxymethyl)-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:958485 CAPLUS
DOCUMENT NUMBER: 144:100402
TITLE: Antiviral activity and safety of 873140, a novel CCR5 antagonist, during short-term monotherapy in HIV-infected adults
AUTHOR(S): Lalezari, Jacob; Thompson, Melanie; Kumar, Priny; Piliero, Peter; Davey, Richard; Patterson, Kristine; Shachoy-Clark, Anne; Adkison, Kimberly; Demarest, James; Lou, Yu; Berrey, Michelle; Piscitelli, Stephen
CORPORATE SOURCE: Quest Clinical Research, San Francisco, CA, USA
SOURCE: AIDS (Hagerstown, MD, United States) (2005), 19(14), 1443-1448
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: 873140 is a spirodiketopiperazine CCR5 antagonist with prolonged receptor binding and potent antiviral activity in vitro. This study evaluated plasma HIV RNA, safety, and pharmacokinetics following short-term monotherapy in HIV-infected adults. Design: Double-blind, randomized, placebo-controlled multi-center trial. Methods: Treatment-naive or experienced HIV-infected subjects with R5-tropic virus, CD4 cell count nadir > 200 + 106 cells/l, viral load > 5000 copies/mL and not receiving antiretroviral therapy for the preceding 12 wk were enrolled. Forty subjects were randomized to one of four cohorts (200 mg QD, 200 mg BID, 400 mg QD, 600 mg BID) with 10 subjects (eight active, two placebo) in each cohort, and received treatment for 10 days. Serial HIV RNA, pharmacokinetics, and safety evaluations were performed through day 24. Results: Of the 40 subjects, 21 were treatment-experienced; 35 were male, 20 were non-white, and eight were coinfected with hepatitis C virus. Median baseline HIV RNA ranged from 4.26log10 to 4.46 log10. 873140 was generally well tolerated with no drug-related discontinuations. The most common adverse events were grade 1 gastrointestinal complaints that generally resolved within 1-3 days on therapy. No clin. significant abnormalities were observed on ECG or in laboratory parameters. Mean log changes in HIV RNA at nadir, and the percentage of subjects with > 1 log10 decrease were -0.12 (0%) for placebo, -0.46 (17%) for 200 mg once daily, -1.23 (75%) for 200 mg twice daily, -1.03 (63%) for 400 mg once daily, and -1.66 (100%) for 600 mg twice daily. An Emax relationship was observed between the area under the 873140 plasma concentration-time curve and change in HIV RNA. Conclusions: 873140 demonstrated potent antiretroviral activity and was well tolerated. These results support further evaluation in Phase 2b/3 studies.

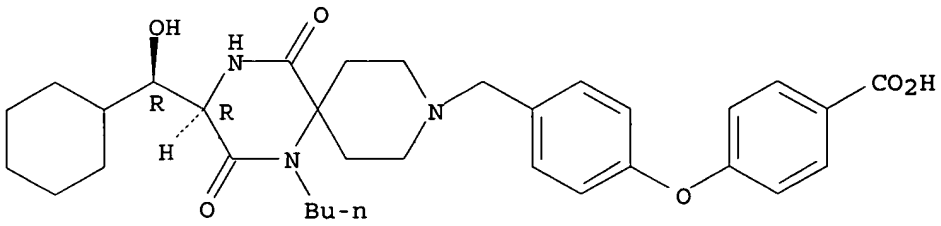
IT 461023-63-2
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(CCR5 antagonist 873140 was safe, well tolerated and effective in HIV-infected patient)

RN 461023-63-2 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:698347 CAPLUS

DOCUMENT NUMBER: 143:194248

TITLE: Therapeutic combinations containing an amino acid amide HIV protease inhibitor

INVENTOR(S): Hammond, Jennifer Lou; Patick, Amy Karen

PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 25 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

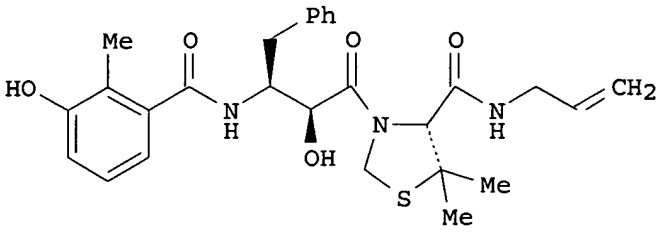
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005171038	A1	20050804	US 2005-46260	20050128
AU 2005216710	A1	20050909	AU 2005-216710	20050117
CA 2555171	AA	20050909	CA 2005-2555171	20050117
WO 2005082362	A1	20050909	WO 2005-IB101	20050117
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1713470	A1	20061025	EP 2005-702264	20050117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				

PRIORITY APPLN. INFO.:

US 2004-540749P	P	20040130
US 2004-615000P	P	20041001
WO 2005-IB101	W	20050117

OTHER SOURCE(S): CASREACT 143:194248
GI



I

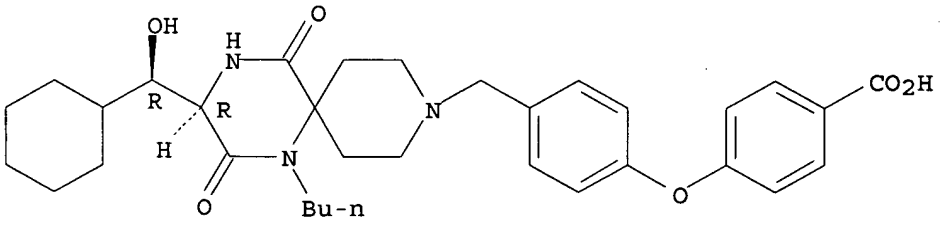
AB The invention is related to methods for treating an HIV infection by using a therapeutically effective amount of a combination of compds., including I and its related N-amide derivs. The invention is also related to compns. comprising certain compds. useful as inhibitors of the HIV protease enzyme and at least one addnl. therapeutic agent. In an XTT dye reduction method, I in combination with ritonavir acted synergistically against HIV-1 infection.

IT 461443-59-4, GW 873140
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy agent; compns. comprising an amino acid amide HIV protease inhibitor)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

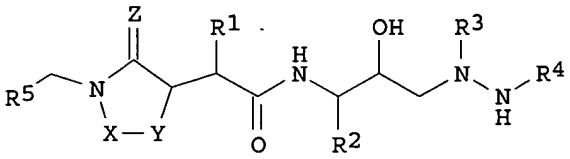


L4 ANSWER 15 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:641882 CAPLUS
DOCUMENT NUMBER: 143:153711
TITLE: Preparation of amino acid hydrazide derivatives as HIV protease inhibitors
INVENTOR(S): Randolph, John T.; Chen, Hui-ju; Degoey, David A.; Flentge, Charles A.; Flosi, William J.; Grampovnik, David J.; Huang, Peggy P.; Hutchinson, Douglas K.; Kempf, Dale J.; Klein, Larry L.; Yeung, Ming C.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 155 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005159469	A1	20050721	US 2004-10177		20041210
PRIORITY APPLN. INFO.:			US 2003-528679P	P	20031211
OTHER SOURCE(S):	MARPAT 143:153711				

GI



I

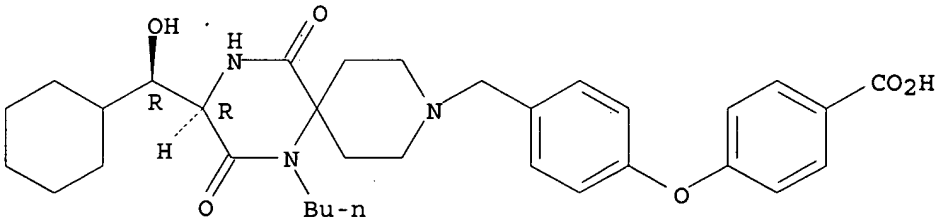
AB The invention relates to amino acid hydrazide derivs. I [X-Y is CH2(CH2)1-2, CH:CH or C(:Z')(CH2)1-2; Z, Z' are O, S or NH; R1, R2, R5 are independently (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, etc.; R3 is H, alkyl, aryl, etc.; R4 is an amino acid or acyl residue of defined structure], including pharmaceutically-acceptable salts, stereoisomers, esters or prodrugs, having HIV protease inhibitory activity. Thus, hydrazide I [X-Y is CH2CH2; Z is O; R1 is CMeEt; R2 is PhCH2; R3 is 4-(2-pyridyl)benzyl; R4 is N-carbomethoxy-tert-leucine (all-S stereo)] was prepared by a multistep sequence involving peptide coupling in the final step. Compds. of the invention showed EC50 values 1-100 nM against wild-type HIV.

IT 461443-59-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid hydrazide derivs. as HIV protease inhibitors)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 16 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2005:590606 CAPLUS
DOCUMENT NUMBER:	143:125797
TITLE:	Pharmacokinetics and short-term safety of 873140, a novel CCR5 antagonist, in healthy adult subjects
AUTHOR(S):	Adkison, Kimberly K.; Shachoy-Clark, Anne; Fang, Lei; Lou, Yu; O'Mara, Kathy; Berrey, M. Michelle; Piscitelli, Stephen C.
CORPORATE SOURCE:	GlaxoSmithKline, Research Triangle Park, NC, USA
SOURCE:	Antimicrobial Agents and Chemotherapy (2005), 49(7), 2802-2806 CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER:	American Society for Microbiology

DOCUMENT TYPE: Journal
LANGUAGE: English

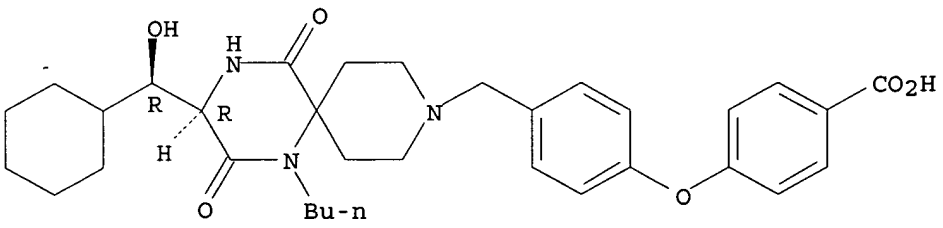
AB 873140 Is a novel CCR5 antagonist with potent in vitro anti-human immunodeficiency virus (HIV) activity. This study was a double-blind, randomized, placebo-controlled, single- and repeat-dose escalation investigation of the safety, pharmacokinetics, and food effect of 873140 in 70 adult subjects. During single-dose escalation, three cohorts (each composed of 10 subjects, with 8 subjects receiving the active drug and 2 subjects receiving the placebo [8 active and 2 placebo]) received doses of 50, 200, 400, 800, and 1,200 mg after an overnight fast, or 400 mg plus a standard high-fat breakfast in an alternating panel design. During repeat-dose escalation, four cohorts (each with 8 active and 2 placebo) received doses of 200, 400, 600, or 800 mg every 12 h (BID) for 8 days. Laboratory safety tests, vital signs, and electrocardiograms (ECGs) were performed at regular intervals, and blood samples were obtained for pharmacokinetics. Single and repeat doses of 50 mg to 800 mg were well tolerated, with no serious adverse events and no grade 3 or 4 adverse events. The mild-to-moderate side effects were primarily gastrointestinal and included abdominal cramping, nausea, and diarrhea. No specific trends in laboratory parameters or clin. significant ECG changes were noted. Plasma 873140 concns. increased rapidly; the median time to maximum concentration of drug in serum was 1.75 to 5 h. The median area under the plasma concentration-time profile (AUC) and the maximum concentration of drug in serum (Cmax) ranged from 127 ng · h/mL and 24 ng/mL at 200 mg BID to 329 ng · h/mL and 100 ng/mL at 800 mg BID, resp. Food consumption increased the AUC and Cmax by a mean of 1.7- and 2.2-fold, resp. The pharmacokinetic and safety profile supports the continued investigation of 873140 with HIV-infected subjects.

IT 461023-63-2
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(pharmacokinetics and short-term safety of 873140, a novel CCR5 antagonist, in healthy adult subjects)

RN 461023-63-2 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:588945 CAPLUS
DOCUMENT NUMBER: 143:133695
TITLE: Preparation of amino acid hydrazide derivatives as HIV protease inhibitors

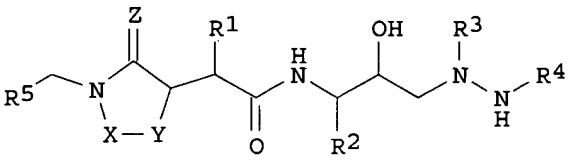
10/527,193

INVENTOR(S): Randolph, John T.; Chen, Hui-Ju; Degoey, David A.; Flentge, Charles A.; Flosi, William J.; Grampovnik, David J.; Huang, Peggy P.; Hutchinson, Douglas K.; Kempf, Dale J.; Klein, Larry L.; Yeung, Ming C.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 281 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005061487	A1	20050707	WO 2004-US37711	20041110
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2549228	AA	20050707	CA 2004-2549228	20041110
EP 1697348	A1	20060906	EP 2004-810778	20041110
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				

PRIORITY APPLN. INFO.: US 2003-733227 A 20031211
WO 2004-US37711 W 20041110

OTHER SOURCE(S): MARPAT 143:133695
GI



I

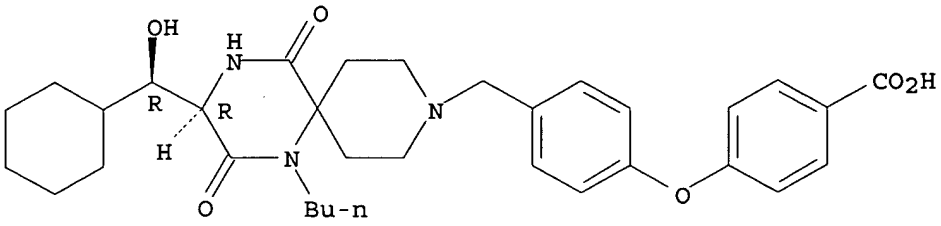
AB The invention relates to amino acid hydrazide derivs. I [X-Y is CH2(CH2)1-2, CH:CH or C(:Z')(CH2)1-2; Z, Z' are O, S or NH; R1, R2, R5 are independently (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, etc.; R3 is H, alkyl, aryl, etc.; R4 is an amino acid or acyl residue of defined structure], including pharmaceutically-acceptable salts, stereoisomers, esters or prodrugs, having HIV protease inhibitory activity. Thus, hydrazide I [X-Y is CH2CH2; Z is O; R1 is CMeEt; R2 is PhCH2; R3 is 4-(2-pyridyl)benzyl; R4 is N-carbomethoxy-tert-leucine (all-S stereo)] was prepared by a multistep sequence involving peptide coupling in the final step. Compds. of the invention showed EC50 values 1-100 nM against wild-type HIV.

IT 461443-59-4, GW873140
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid hydrazide derivs. as HIV protease inhibitors)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:588404 CAPLUS
DOCUMENT NUMBER: 143:133693
TITLE: Preparation of amino acid derivatives as HIV protease inhibitors
INVENTOR(S): Degoey, David A.; Flentge, Charles A.; Flosi, William J.; Grampovnik, David J.; Kempf, Dale J.; Klein, Larry L.; Yeung, Ming C.; Randolph, John T.; Wang, Xiu C.; Yu, Su
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 279 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005148623	A1	20050707	US 2004-8713		20041209
PRIORITY APPLN. INFO.:			US 2003-528974P	P	20031211

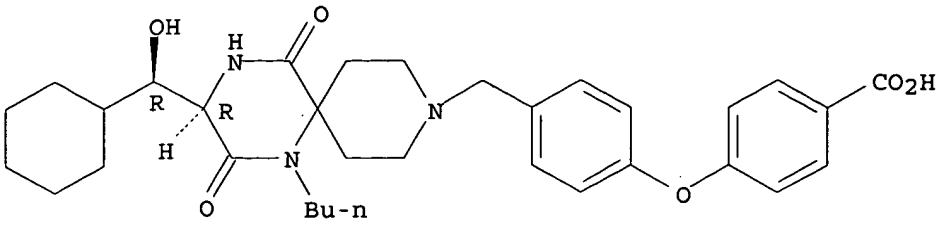
OTHER SOURCE(S): MARPAT 143:133693

AB The invention relates to amino acid derivs. A-NHCHR6CHR5CHR4CHR3NHCOCHR2NHCO2R1 [A is an amino acid or acyl residue of defined structure; R1, R2, R3, R6 are independently (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl or heteroaryl; R4, R5 are H (not both), OH or substituted hydroxyl], including pharmaceutically-acceptable salts, prodrugs or stereoisomers, having HIV protease inhibitory activity. Thus, Me (1S,4R,6S,7S,10S)-7-benzyl-1,10-di-tert-butyl-6-hydroxy-2,9,12-trioxo-4-[4-(2-pyridinyl)benzyl]-13-oxa-3,8,11-triazatetradec-1-ylcarbamate was prepared by a multistep procedure, which includes the reaction of intermediate tert-Bu (1S,2S,4R)-4-amino-1-benzyl-2-hydroxy-5-[4-(2-pyridinyl)phenyl]pentylcarbamate with N-protected L-tert-leucine. Compds. of the invention showed EC50 values in the range 0.7 nM to >3.2 μM against wild-type HIV.

IT 461443-59-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid derivs. as HIV protease inhibitors)

RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



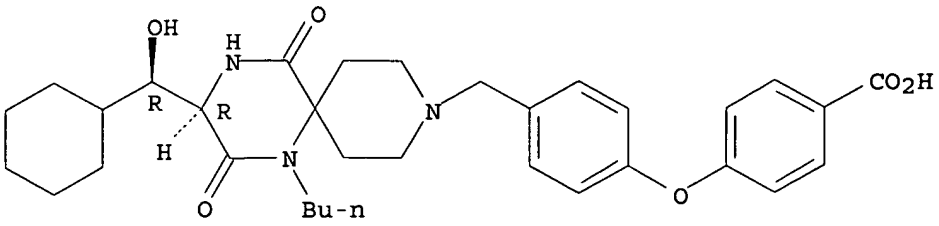
L4 ANSWER 19 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:536932 CAPLUS
DOCUMENT NUMBER: 143:125633
TITLE: The appealing story of HIV entry inhibitors: from discovery of biological mechanisms to drug development
AUTHOR(S): Castagna, Antonella; Biswas, Priscilla; Beretta, Alberto; Lazzarin, Adriano
CORPORATE SOURCE: Clinic of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy
SOURCE: Drugs (2005), 65(7), 879-904
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Current therapeutic intervention in HIV infection relies upon 20 different drugs. Despite the impressive efficacy shown by these drugs, we are confronted with an unexpected frequency of adverse effects, such as mitochondrial toxicity and lipodystrophy, and resistance, not only to individual drugs but to entire drug classes. Thus, there is now a great need for new antiretroviral drugs with reduced toxicity, increased activity against drug-resistant viruses and a greater capacity to reach tissue sanctuaries of the virus. Two different HIV mols. have been selected as targets of drug inhibition so far: reverse transcriptase and protease. Drugs that target the interactions between the HIV envelope and the cellular receptor complex are a 'new entry' into the scenario of HIV therapy and have recently raised great interest because of their activity against multidrug-resistant viruses. There are several compds. that are at different developmental stages in the pipeline to counter HIV entry, among them: (i) the attachment inhibitor dextrin-2-sulfate; (ii) the inhibitors of the glycoprotein (gp) 120/CD4 interaction PRO 542, TNX 355 and BMS 488043; (iii) the co-receptor inhibitors subdivided in those targeting CCR5 (SCH 417690 [SCH D], UK 427857 GW 873140, PRO 140, TAK 220, AMD 887) and those targeting CXCR4 (AMD 070, KRH 2731); and (iv) the fusion inhibitors; enfuvirtide (T-20) and tifuvirtide (T-1249). The story, of the first of these drugs, enfuvirtide, which has successfully completed phase III clin. trials, has been approved by the US FDA and by the European Medicines Agency, and is now com. available worldwide, is an example of how the knowledge of basic mol. mechanisms can rapidly translate into the development of clin. effective mols.

IT 461443-59-4, GW 873140
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(addition of co-receptor CCR5 inhibitor GW 873140 to therapeutic armamentarium against HIV-1 offers new hope for treating HIV infected patient)

RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 198 THERE ARE 198 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:527407 CAPLUS
DOCUMENT NUMBER: 143:59982
TITLE: Preparation of HIV protease inhibitors, in particular imidazolidine derivatives
INVENTOR(S): Flentge, Charles A.; Chen, Hui-Ju; Degoey, David A.; Flosi, William J.; Grampovnik, David J.; Huang, Peggy P.; Kempf, Dale J.; Klein, Larry L.; Krueger, Allan C.; Madigan, Darold L.; Randolph, John T.; Sun, Minghua; Yeung, Ming C.; Zhao, Chen
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 287 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005131042	A1	20050616	US 2003-733915	20031211
CA 2549389	AA	20050707	CA 2004-2549389	20041110
WO 2005061450	A2	20050707	WO 2004-US37745	20041110
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1709037	A2	20061011	EP 2004-810802	20041110
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				

PRIORITY APPLN. INFO.: US 2003-733915 A 20031211
WO 2004-US37745 W 20041110
OTHER SOURCE(S): MARPAT 143:59982
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

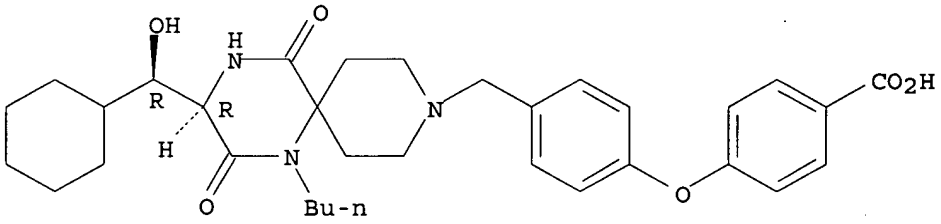
AB Title compds. of formula ANH(CHR)(CHR1)(CHR2)NR3S(O2)R4 (I) [wherein A = alkylcarbonyl, arylsulfonyl, 1,3-substituted 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, etc.; X, Y = independently O, S, NH; R = (un)substituted alk(en)yl, cycloalk(en)yl, hetero/arylalkyl, etc.; R1 = OH and derivs., OPO3H and derivs., OSO2H and derivs., etc.; R2 = H; R3 = halo/alkyl, halo/alkenyl, (un)substituted cycloalk(en)yl, aryl; R4 = (un)substituted cycloalk(en)yl, heterocyclyl, hetero/aryl] were prepared as HIV protease inhibitors. For example, II was prepared, in 62% yield, by coupling acid III (preparation given) with amine IV (preparation given). I showed antiviral activity against Wild-Type HIV with EC50 in the range of 1 nM to 100 nM.

IT 461443-59-4, GW873140
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; preparation of HIV protease inhibitors, in particular imidazolidine derivs.)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 21 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:527398 CAPLUS
DOCUMENT NUMBER: 143:78485
TITLE: Preparation of amino acid derivatives as HIV protease inhibitors
INVENTOR(S): Degoey, David A.; Flentge, Charles A.; Flosi, William J.; Grampovnik, David J.; Kempf, Dale J.; Klein, Larry L.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 204 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005131017	A1	20050616	US 2003-733946	20031211
CA 2549098	AA	20050630	CA 2004-2549098	20041209
WO 2005058841	A2	20050630	WO 2004-US41658	20041209
WO 2005058841	A3	20060309		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1697344 A2 20060906 EP 2004-813910 20041209

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU

PRIORITY APPLN. INFO.: US 2003-733946 A 20031211
WO 2004-US41658 W 20041209

OTHER SOURCE(S): MARPAT 143:78485

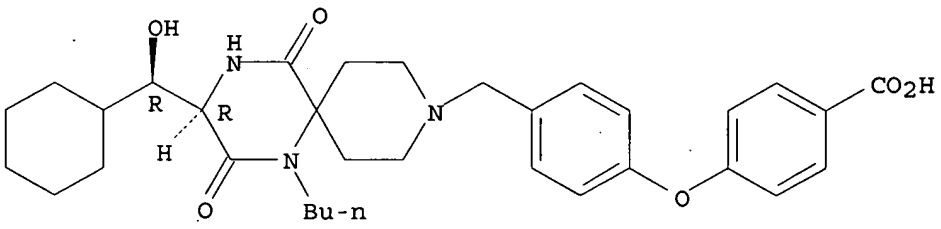
AB The invention relates to amino acid derivs. A-NHCHR6CHR5CHR4CHR3NHCOCHR2NHCO2R1 [A is an amino acid or acyl residue of defined structure; R1, R2, R3, R6 are independently (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl or heteroaryl; R4, R5 are H (not both), OH or substituted hydroxyl], including pharmaceutically-acceptable salts, stereoisomers, esters or prodrugs, having HIV protease inhibitory activity. Thus, Me (1S,4R,6S,7S,10S)-7-benzyl-1,10-di-tert-butyl-6-hydroxy-2,9,12-trioxo-4-[4-(2-pyridinyl)benzyl]-13-oxa-3,8,11-triazatetradec-1-ylcarbamate was prepared by a multistep procedure, which includes the reaction of intermediate tert-Bu (1S,2S,4R)-4-amino-1-benzyl-2-hydroxy-5-[4-(2-pyridinyl)phenyl]pentylcarbamate with N-protected L-tert-leucine. Compds. of the invention showed EC50 values 0.7-300 nM against wild-type HIV.

IT 461443-59-4, GW873140
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid derivs. as HIV protease inhibitors)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:311526 CAPLUS

DOCUMENT NUMBER: 142:456334

TITLE: The CCR5 receptor-based mechanism of action of 873140, a potent allosteric noncompetitive HIV entry inhibitor

AUTHOR(S): Watson, Christian; Jenkinson, Stephen; Kazmierski, Wieslaw; Kenakin, Terry

CORPORATE SOURCE: Assay Development and Compound Profiling, GlaxoSmithKline Research and Development, Research Triangle Park, NC, USA

SOURCE: Molecular Pharmacology (2005), 67(4), 1268-1282
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 4-{[4-({(3R)-1-Butyl-3-[(R)-cyclohexyl(hydroxy)methyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl}methyl)phenyl]oxy}benzoic acid hydrochloride

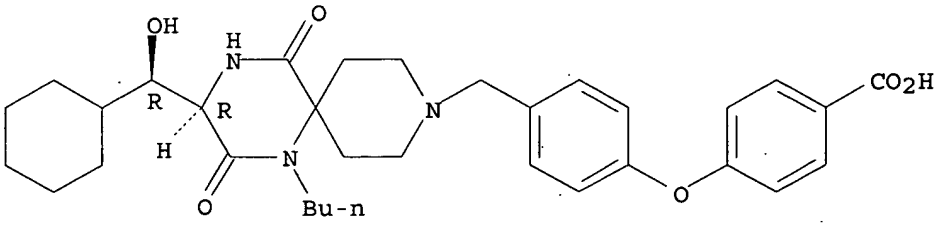
(873140) is a potent noncompetitive allosteric antagonist of the CCR5 receptor (pKB = 8.6±0.07; 95% Cl, 8.5 to 8.8) with concomitantly potent antiviral effects for HIV-1. In this article, the receptor-based mechanism of action of 873140 is compared with four other noncompetitive allosteric antagonists of CCR5. Although (Z)-(4-bromophenyl){1'-[(2,4-dimethyl-1-oxido-3-pyridinyl)carbonyl]-4'-methyl-1,4'-bipiperidin-4-yl}methanone O-ethyloxime (Sch-C; SCH 351125), 4,6-dimethyl-5-{[4-methyl-4-((3S)-3-methyl-4-{(1R)-2-(methyloxy)-1-[4-(trifluoromethyl)phenyl]ethyl}-1-piperazinyl)-1-piperidinyl]carbonyl}pyrimidine (Sch-D; SCH 417,690), 4,4-difluoro-N-((1S)-3-{(3-endo)-3-[3-methyl-5-(1-methylethyl)-4H-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]oct-8-yl}-1-phenylpropyl)cyclohexanecarboxamide (UK-427,857), and N,N-dimethyl-N-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclo-hepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2H-pyran-4-aminium chloride (TAK779) blocked the binding of both chemokines 125I-MIP-1α (also known as 125I-CCL3, 125I-LD78) and 125I-RANTES (125I-CCL5), 873140 was an ineffectual antagonist of 125I-RANTES (regulated on activation normal T cell expressed and secreted) binding (but did block binding of 125I-MIP-1α). Furthermore, 873140 blocked the calcium response effects of CCR5 activation by CCL5 (RANTES) (as did the other antagonists), indicating a unique divergence of blockade of function and binding with this antagonist. The antagonism of CCR5 by 873140 is saturable and probe-dependent, consistent with an allosteric mechanism of action. The blockade of CCR5 by 873140 was extremely persistent with a rate constant for reversal of <0.004 h-1 (t1/2 > 136 h). Coadministration studies of 873140 with the four other allosteric antagonists yielded data that are consistent with the notion that all five of these antagonists bind to a common allosteric site on the CCR5 receptor. Although these ligands may have a common binding site, they do not exert the same allosteric effect on the receptor, as indicated by their differential effects on the binding of 125I-RANTES. This idea is discussed in terms of using these drugs sequentially to overcome HIV viral resistance in the clinic.

IT 461023-63-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(873140; CCR5 receptor-based mechanism of action of compound 873140, a potent allosteric noncompetitive HIV entry inhibitor)

RN 461023-63-2 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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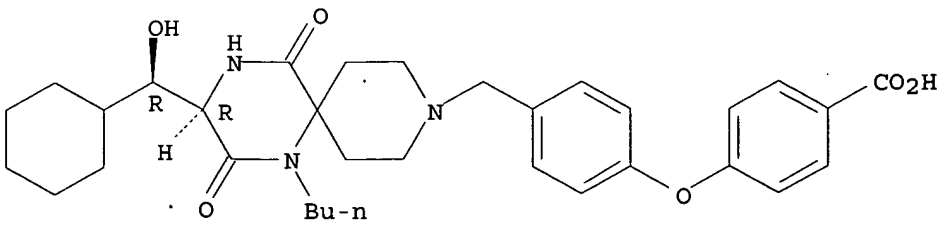
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:233058 CAPLUS
DOCUMENT NUMBER: 142:366839
TITLE: Potent anti-R5 human immunodeficiency virus type 1 effects of a CCR5 antagonist, AK602/ONO4128/GW873140, in a novel human peripheral blood mononuclear cell nonobese diabetic-SCID, interleukin-2 receptor γ-chain-knocked-out AIDS mouse model
AUTHOR(S): Nakata, Hirotomo; Maeda, Kenji; Miyakawa, Toshikazu; Shibayama, Shiro; Matsuo, Masayoshi; Takaoka, Yoshikazu; Ito, Mamoru; Koyanagi, Yoshio; Mitsuya, Hiroaki
CORPORATE SOURCE: Department of Infectious Diseases, Kumamoto University Graduate School of Medicine, Kumamoto, 860-8556, Japan
SOURCE: Journal of Virology (2005), 79(4), 2087-2096
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We established human peripheral blood mononuclear cell (PBMC)-transplanted R5 human immunodeficiency virus type 1 isolate JR-FL (HIV-1JR-FL)-infected, nonobese diabetic-SCID, interleukin 2 receptor γ-chain-knocked-out (NOG) mice, in which massive and systemic HIV-1 infection occurred. The susceptibility of the implanted PBMC to the infectivity and cytopathic effect of R5 HIV-1 appeared to stem from hyperactivation of the PBMC, which rapidly proliferated and expressed high levels of CCR5. When a novel spirodiketopiperazine-containing CCR5 inhibitor, AK602/ONO4128/GW873140 (mol. weight, 614), was administered to the NOG mice 1 day after R5 HIV-1 inoculation, the replication and cytopathic effects of R5 HIV-1 were significantly suppressed. In saline-treated mice (n = 7), the mean human CD4+/CD8+ cell ratio was 0.1 on day 16 after inoculation, while levels in mice (n = 8) administered AK602 had a mean value of 0.92, comparable to levels in uninfected mice (n = 7). The mean number of HIV-RNA copies in plasma in saline-treated mice were .apprx.106/mL on day 16, while levels in AK602-treated mice were 1.27+103/mL (P = 0.001). AK602 also significantly suppressed the number of proviral DNA copies and serum p24 levels (P = 0.001). These data suggest that the present NOG mouse system should serve as a small-animal AIDS model and warrant that AK602 be further developed as a potential therapeutic for HIV-1 infection.
IT 461443-59-4, AK602
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-R5 HIV1 activity of CCR5 antagonist, AK602, in novel PBMC diabetic-SCID, IL-2R-knocked-out AIDS mouse model)
RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:160977 CAPLUS
DOCUMENT NUMBER: 142:246180
TITLE: Pharmaceutical compositions comprising CCR5 antagonists
INVENTOR(S): Peled, Amnon; Wald, Ori; Galun, Eithan
PATENT ASSIGNEE(S): Hadasit Medical Research Services & Development Ltd., Israel
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005016226	A2	20050224	WO 2004-IL743	20040812
WO 2005016226	A3	20060803		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

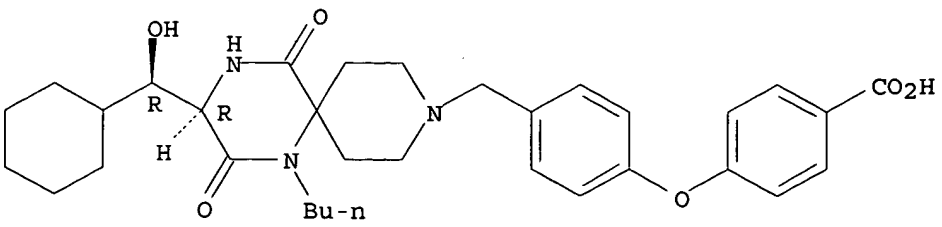
PRIORITY APPLN. INFO.: IL 2003-157398 A 20030814

AB A pharmaceutical composition comprising at least one CCR5 antagonist, such as anti-CCR5 antibodies, modified chemokines or a fraction thereof, peptides derived from such chemokines, and small organic mols., e.g., TAK 220, SCH C, SCH D, AK 602 or UK 427857, and a a pharmaceutically acceptable carrier is useful for reducing liver inflammation and liver damage caused by HCV infection. The pharmaceutical composition comprising CCR5 antagonists is useful for administration together with combined interferon-α and ribavirin therapy.

IT 461443-59-4, AK 602
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising CCR5 antagonists for treatment of liver diseases)

RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

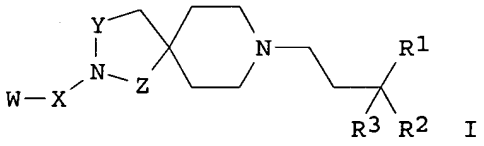


L4 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:74120 CAPLUS

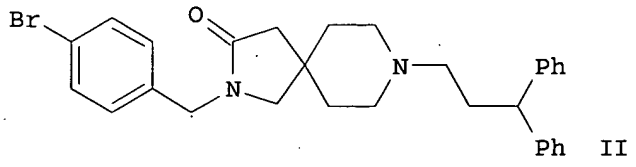
DOCUMENT NUMBER: 142:176697
TITLE: Preparation of spiro compounds for the modulation of chemokine receptor activity
INVENTOR(S): Chan, Chun Kong; Zhang, Ming-Qiang; Moinet, Christophe; Proulx, Melanie; Reddy, Thumkunta Jagadeeswar; Courchesne, Marc
PATENT ASSIGNEE(S): Virochem Pharma Inc., Can.
SOURCE: PCT Int. Appl., 338 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005007656	A1	20050127	WO 2004-CA1048	20040716
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005075326	A1	20050407	US 2004-893583	20040719

PRIORITY APPLN. INFO.: US 2003-487973P P 20030718
OTHER SOURCE(S): MARPAT 142:176697
GI



I



II

AB The title compds. I [Y, Z and X = CH2, CO, CR4R5; W = H, alkyl, alkenyl, aryl, etc.; R1 = H, OH, alkyl, etc.; R2 = alkyl, alkenyl, alkynyl, aryl, heterocyclyl; R3 = H, alkyl, alkenyl, alkynyl, aryl; R4, R5 = H, alkyl, alkenyl, alkynyl, aryl] and their pharmaceutically acceptable salts, useful for the modulation of CCR5 chemokine receptor activity and the treatment or prevention of diseases associated therewith, were prepared E.g., a multi-step synthesis of II.HCl, starting from tert-Bu 1-oxo-2,8-diaza-spiro[4.5]decane-8-carboxylate and 4-bromobenzyl bromide, was given. The compds. I have been found to have activity in binding to the CCR5 receptor, generally with an IC50 values of < 25 μM. Certain

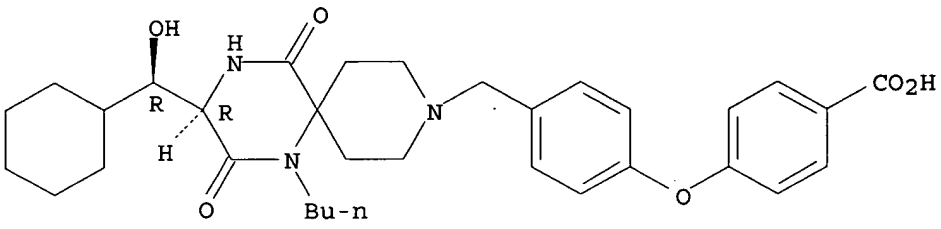
compds. I have also been tested in an assay for HIV activity, and generally having an IC50 values of < 1 μM.

IT 461443-59-4, Ak602
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-drug; preparation of spiro compds. for treating diseases associated with CCR5 chemokine receptor activity in combination with other agents)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:14522 CAPLUS
DOCUMENT NUMBER: 142:86614
TITLE: Compositions for down-regulation of CCR5 expression and reducing HIV entry into T-cells
INVENTOR(S): Redfield, Robert R.; Amoroso, Anthony; Davis, Charles E.; Heredia, Alonsa
PATENT ASSIGNEE(S): University of Maryland Biotechnology Institute, USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005001027	A2	20050106	WO 2004-US15681	20040517
WO 2005001027	A3	20060126		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004251228	A1	20050106	AU 2004-251228	20040517
CA 2526122	AA	20050106	CA 2004-2526122	20040517
EP 1627048	A2	20060222	EP 2004-752660	20040517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1805740	A	20060719	CN 2004-80016720	20040517
BR 2004010360	A	20060801	BR 2004-10360	20040517

US 2006154857	A1	20060713	US 2005-281195	20051116
PRIORITY APPLN. INFO.:			US 2003-471453P	P 20030516
			WO 2004-US15681	W 20040517

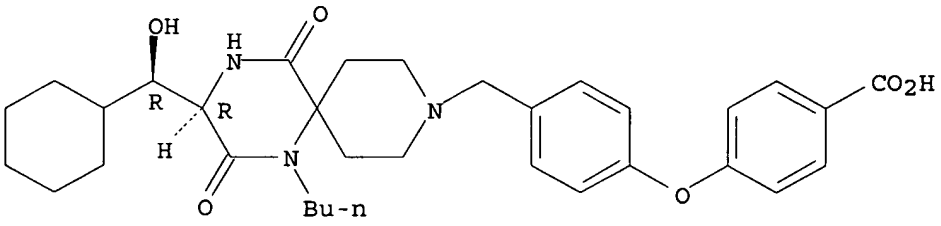
AB The present invention relates to the downregulation of surface receptor CCR5 expression through manipulation of the cell cycle in activated lymphocytes by administering a composition that arrests the G1 phase of the cell cycle, thereby reducing receptor sites for entry of HIV into T cells, and thus, the effects of HIV. Further, a composition is disclosed that includes a G1 phase arresting agent and an antiviral agent, wherein the combination synergically enhances the activity of the antiviral agent.

IT 461443-59-4, Ak602
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for down-regulation of CCR5 expression and reducing HIV entry into T-cells)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2004:996006 CAPLUS
DOCUMENT NUMBER:	141:406151
TITLE:	Effector cell function inhibitor
INVENTOR(S):	Shibayama, Shiro; Sugiyama, Tetsuya; Sagawa, Kenji; Kasano, Miki
PATENT ASSIGNEE(S):	Ono Pharmaceutical Co., Ltd., Japan
SOURCE:	PCT Int. Appl., 114 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	Japanese
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004098638	A1	20041118	WO 2004-JP6197	20040428
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1623721	A1	20060208	EP 2004-730075	20040428
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

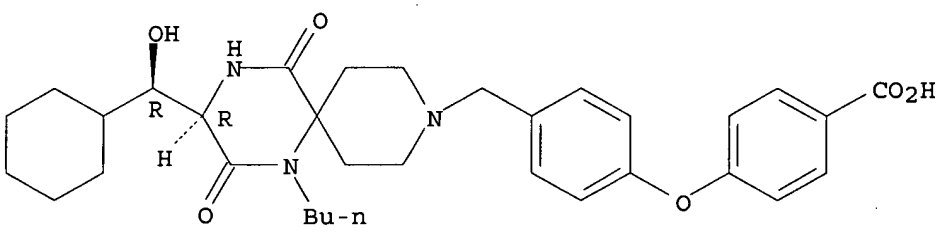
IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK
PRIORITY APPLN. INFO.: JP 2003-128193 A 20030506
WO 2004-JP6197 W 20040428
OTHER SOURCE(S): MARPAT 141:406151

AB An effector cell function inhibitor comprised of CCR5-antagonist. The effector cell function inhibitor comprised of CCR5-antagonist is capable of inhibiting the function of effector cells playing an important roll in disease generation, etc., so that it is useful in the prevention and/or treatment of, for example, transplant rejections (rejection of solid organ graft, rejection of pancreatic cell transplant in diabetes, graft-vs.-host disease (GVHD), etc.), autoimmune diseases (arthritis, chronic arthritic rheumatism, multiple sclerosis, ulcerative colitis, etc.), allergoses (asthma, etc.), ischemic diseases (ischemia reperfusion lesion, etc.), cancer or cancer metastasis, etc.

IT 461023-63-2 676451-07-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of cyclohexyldioxotriazaspiroundecaylmethylphenoxybenzoate analogs as CCR5 antagonists and effector cell function inhibitors)

RN 461023-63-2 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

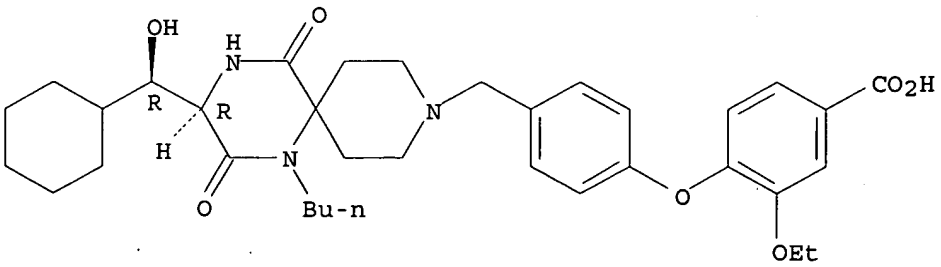
Absolute stereochemistry.



● HCl

RN 676451-07-3 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-3-ethoxy-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

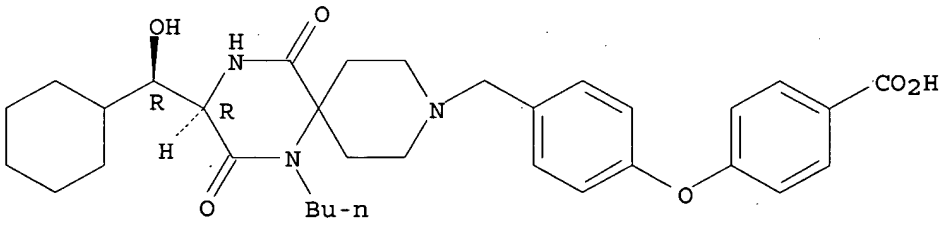
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:875343 CAPLUS
DOCUMENT NUMBER: 142:147626
TITLE: GW-873140
AUTHOR(S): McIntyre, J. A.; Castaner, J.
CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (2004), 29(7), 677-679
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The human immunodeficiency virus (HIV) is a highly mutative virus, representing a challenge for researchers in terms of the development of effective therapeutic strategies against HIV and AIDS. HIV entry inhibitors block the fusion of HIV with host cells and are not compromised by the process of viral resistance, implicit with many anti-HIV therapies. The R5 viral strain is the most prevalent viral type isolated from asymptomatic individuals and its coreceptor CCR5 is blocked by GW-873140 (Ono-4128, AK-602). GW-873140 demonstrated potent activity against a wide spectrum of laboratory and primary HIV R5 isolates, and anti-HIV activity was observed for up to 24 h following binding to CCR5. This was also demonstrated in a phase I study in healthy adult subjects, with prolonged CCR5 receptor occupancy despite plasma levels of GW-873140 at or below the assay detection limit. The drug was well tolerated in this study and is entering phase II testing.

IT 461443-59-4P, GW873140
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(GW-873140 for treatment of HIV injection)
RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

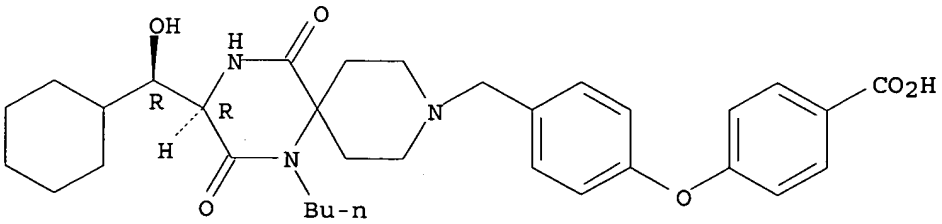


REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:670576 CAPLUS
DOCUMENT NUMBER: 141:235755
TITLE: Spirodiketopiperazine-based CCR5 inhibitor which preserves CC-chemokine/CCR5 interactions and exerts potent activity against R5 human immunodeficiency virus type 1 in vitro
AUTHOR(S): Maeda, Kenji; Nakata, Hirotomo; Koh, Yasuhiro; Miyakawa, Toshikazu; Ogata, Hiromi; Takaoka, Yoshikazu; Shibayama, Shiro; Sagawa, Kenji; Fukushima,

Daikichi; Moravek, Joseph; Koyanangi, Yoshio; Mitsuya, Hiroaki
CORPORATE SOURCE: Dep. Hematol., Kumamoto Univ. Sch. Med., Kumamoto, 860-8556, Japan
SOURCE: Journal of Virology (2004), 78(16), 8654-8662
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We identified a novel spirodiketopiperazine (SDP) derivative, AK602/ONO4128/GW873140, which specifically blocked the binding of macrophage inflammatory protein 1α (MIP-1α) to CCR5 with a high affinity (Kd of ≈3 nM), potently blocked human immunodeficiency virus type 1 (HIV-1) gp120/CCR5 binding and exerted potent activity against a wide spectrum of laboratory and primary R5 HIV-1 isolates, including multidrug-resistant HIV-1 (HIV-1MDR) (50% inhibitory concentration values of 0.1 to 0.6 nM) in vitro. AK602 competitively blocked the binding to CCR5 expressed on Chinese hamster ovary cells of two monoclonal antibodies, 45523, directed against multidomain epitopes of CCR5, and 45531, specific against the C-terminal half of the second extracellular loop (ECL2B) of CCR5. AK602, despite its much greater anti-HIV-1 activity than other previously published CCR5 inhibitors, including TAK-779 and SCH-C, preserved RANTES (regulated on activation normal T-cell expressed and secreted) and MIP-1β binding to CCR5+ cells and their functions, including CC-chemokine-induced chemotaxis and CCR5 internalization, while TAK-779 and SCH-C fully blocked the CC-chemokine/CCR5 interactions. Pharmacokinetic studies revealed favorable oral bioavailability in rodents. These data warrant further development of AK602 as a potential therapeutic for HIV-1 infection.
IT 461443-59-4, AK 602
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ONO 4128, GW 873140; spirodiketopiperazine-based CCR5 inhibitor which preserves CC-chemokine/CCR5 interactions and exerts potent activity against R5 human immunodeficiency virus type 1 in vitro)
RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 30 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:531388 CAPLUS
DOCUMENT NUMBER: 141:82353
TITLE: Antagonist and agonist binding to strong binding site of chemokine receptor
INVENTOR(S): Shibayama, Shiro; Sagawa, Kenji; Watanabe, Noriki; Takeda, Kazuhiko; Tada, Hideaki; Fukushima, Daikichi

PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004054616	A1	20040701	WO 2003-JP15973	20031212
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003289329	A1	20040709	AU 2003-289329	20031212
EP 1570860	A1	20050907	EP 2003-780739	20031212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: JP 2002-363013 A 20021213
WO 2003-JP15973 W 20031212

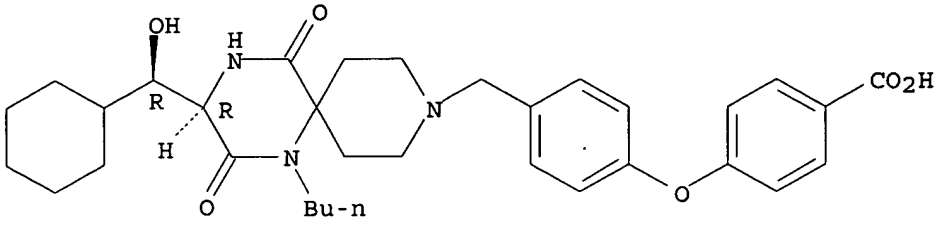
AB An antagonist or an agonist binding to the strong binding site of CCR5; a preventive and/or a remedy for allergic diseases, inflammatory diseases, immune diseases and/or cancerous diseases containing the same; a method of screening a compound binding to the strong binding site of CCR5; a preventive and/or a remedy for allergic diseases, inflammatory diseases, immune diseases and/or cancerous diseases containing the antagonist or the agonist selected by the screening method; an antagonist or an agonist binding to the strong binding site of a chemokine receptor; a preventive and/or a remedy for allergic diseases, inflammatory diseases, immune diseases and/or cancerous diseases containing the same; a method of screening a compound binding to the strong binding site of a chemokine receptor; and a preventive and/or a remedy for allergic diseases, inflammatory diseases, immune diseases and/or cancerous diseases containing the antagonist or the agonist selected by the screening method. These antagonists or agonists are useful as preventives and/or remedies for allergic diseases, inflammatory diseases, immune diseases and/or cancerous diseases.

IT 461023-63-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonists and agonists binding to strong binding site of chemokine receptors as antiinflammatory, immunosuppressants, and antitumor agents)

RN 461023-63-2 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:333850 CAPLUS
DOCUMENT NUMBER: 140:355836
TITLE: High-mannose oligosaccharide cluster conjugated with immunogenic protein for use as HIV vaccines
INVENTOR(S): Wang, Lai-xi
PATENT ASSIGNEE(S): University of Maryland Biotechnology Institute Off. of Research Admin./ Tech. Dev., USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004033663	A2	20040422	WO 2003-US32496	20031014
WO 2004033663	A3	20060316		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2504755	AA	20040422	CA 2003-2504755	20031014
AU 2003282821	A1	20040504	AU 2003-282821	20031014
EP 1572963	A2	20050914	EP 2003-774819	20031014
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005244424	A1	20051103	US 2005-531124	20050630
PRIORITY APPLN. INFO.:			US 2002-417764P P	20021011
			WO 2003-US32496 W	20031014

AB The present invention relates to a constructed oligosaccharide cluster, optionally bonded to an immunogenic protein, that can be administered to a subject to induce an immune response for increasing production of 2G12 and/or used in assays as reactive sites for determining compds. that inactivate and/or bind the high-mannose oligosaccharide cluster. The high-mannose oligosaccharide cluster comprises ≥2 high-mannose oligosaccharides attached a scaffolding framework of monosaccharide, cyclic peptide, cyclic organic compound or 11-bis-maleimidetetraethyleneglycol. The high-mannose

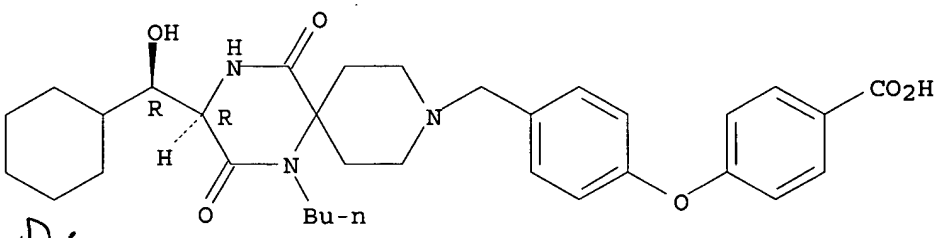
oligosaccharide that mimics high-mannose N-glycan of HIV-1 gp120 comprises Man9, Man8, Man7, Man6, Man5 or a combination thereof. The high-mannose oligosaccharide of the invention is derived from soybean agglutinin or chemical synthesized. The immunogenic protein is keyhole limpet hemocyanin, tetanus toxoid, diphtheria toxoid, bovine serum albumin, ovalbumin, thyroglobulin, myoglobin, cholera toxin β-subunit, Ig. and/or tuberculosis purified protein derivative Compns. comprising these clusters, methods of using these clusters and compns. are disclosed.

IT 461443-59-4, AK 602
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(high-mannose oligosaccharide cluster conjugated with immunogenic protein for use as HIV vaccines)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2004:267337 CAPLUS
DOCUMENT NUMBER:	140:309368
TITLE:	Novel crystals of triazaspiro[5.5]undecane derivative
INVENTOR(S):	Takaoka, Yoshikazu; Okamoto, Masaki; Genba, Yuichi
PATENT ASSIGNEE(S):	Ono Pharmaceutical Co., Ltd., Japan
SOURCE:	PCT Int. Appl., 96 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	Japanese
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004026874	A1	20040401	WO 2003-JP11835	20030917
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003271057	A1	20040408	AU 2003-271057	20030917
EP 1541573	A1	20050615	EP 2003-751273	20030917
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2006052407	A1	20060309	US 2005-527193	20050310
PRIORITY APPLN. INFO.:			JP 2002-272079 A	20020918
			WO 2003-JP11835 W	20030917

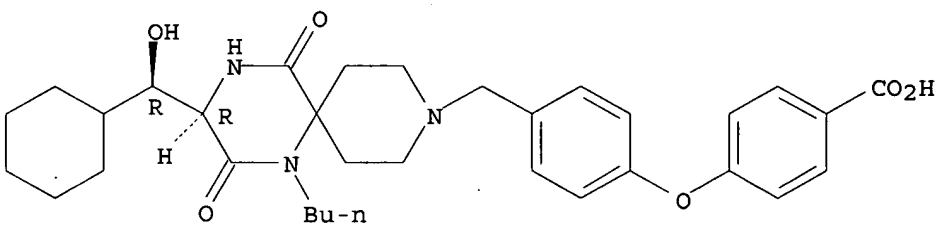
AB Claimed are crystals of non-solvated (3R)-1-butyl-2,5-dioxo-3-((1R)-1-hydroxy-1-cyclohexylmethyl)-9-(4-(4-carboxyphenyloxy)phenylmethyl)-1,4,9-triazaspiro[5.5]undecane hydrochloride. These crystals have a potent antagonism to chemokine/chemokine receptors. Owing to these characteristics, they are useful in producing preventives and/or remedies for various inflammatory diseases, etc. Formulations containing the above crystals are given.

IT 461023-63-2P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of crystals of triazaspiro[5.5]undecane derivative with chemokine antagonist activity)

RN 461023-63-2 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



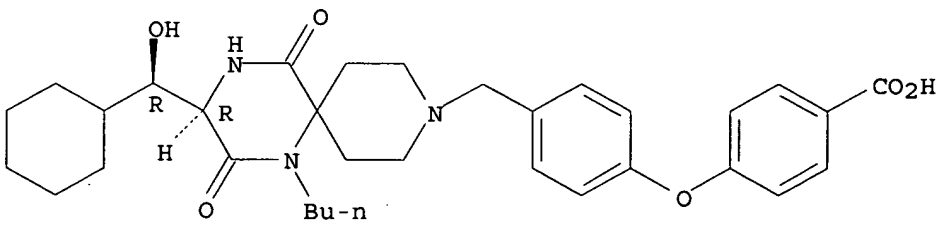
● HCl

IT 461443-59-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of crystals of triazaspiro[5.5]undecane derivative with chemokine antagonist activity)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



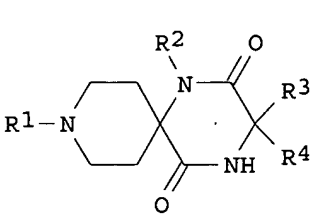
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:267336 CAPLUS

DOCUMENT NUMBER: 140:303699
TITLE: Preparation of triazaspiro[5.5]undecane derivatives as chemokine receptor CCR5 antagonists and drugs comprising the same as the active ingredients
INVENTOR(S): Takaoka, Yoshikazu; Nishizawa, Rena; Shibayama, Shiro; Sagawa, Kenji; Matsuo, Masayoshi
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 288 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004026873	A1	20040401	WO 2003-JP11834		20030917
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2497903	AA	20040401	CA 2003-2497903		20030917
AU 2003272879	A1	20040408	AU 2003-272879		20030917
EP 1541574	A1	20050615	EP 2003-753933		20030917
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003014304	A	20050726	BR 2003-14304		20030917
CN 1688577	A	20051026	CN 2003-824386		20030917
US 2005267114	A1	20051201	US 2005-527435		20050311
NO 2005001379	A	20050617	NO 2005-1379		20050316
ZA 2005002222	A	20050930	ZA 2005-2222		20050316
PRIORITY APPLN. INFO.:			JP 2002-270849	A	20020918
			WO 2003-JP11834	W	20030917

OTHER SOURCE(S): MARPAT 140:303699
GI



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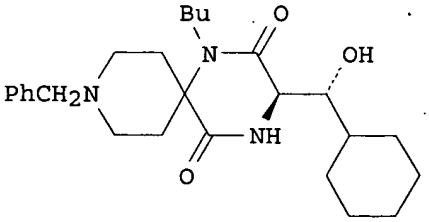


II

AB The title compds. [I; R1 = (a) each (un)substituted and partially or completely saturated C3-15 mono-, di-, or tricarbocyclic aryl or 3- to 15-membered mono-, di-, or triheterocyclic aryl latter containing heteroatoms selected from 1-4 N atoms, 1 or 2 O atoms, and/or 1 or 2 S atoms, or (b) C1-8 alkyl, C2-4 alkenyl, or C2-4 alkynyl each substituted by 1-3 substituents selected from each (un)substituted HO, acyl, NH2, CONH2, acylamino, sulfonylamino, :NH, and :NOH; R2 = H, C1-8 alkyl, C2-8 alkenyl,

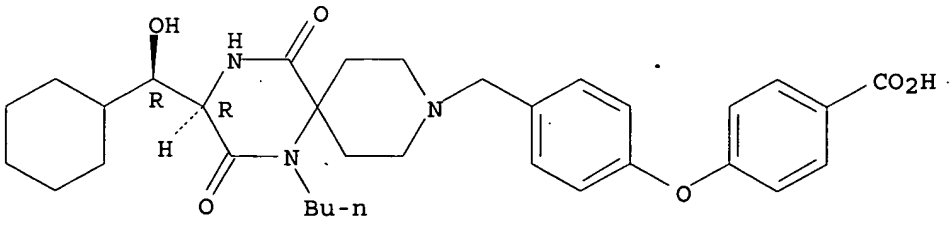
C2-8 alkynyl, each (un)substituted Ph, pyridinyl, or C3-8 cycloalkyl, group (b); R3, R4 = (i) H, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, or (ii) C1-8 alkyl, C2-8 alkenyl, or C2-8 alkynyl each substituted by 1-5 substituents selected from group (a), HO, and tetrahydropyran-4-ylidene], quaternary ammonium salts, N-oxides, or salts thereof are prepared These compds. are useful in preventing and/or treating various inflammatory diseases (asthma, nephritis, nephropathy, hepatitis, arthritis, rheumatoid arthritis, rhinitis, conjunctivitis, ulcerative colitis, etc.), immune diseases (autoimmune disease, transplant rejection, immune suppression, psoriasis, multiple sclerosis, etc.), infection with human immunodeficiency virus (acquired immune deficiency syndrome), allergic diseases (atopic dermatitis, urticaria, allergic bronchopulmonary aspergillosis, allergic eosinophilic gastroenteritis, etc.), ischemic reperfusion injury, acute respiratory distress syndrome, shock accompanying bacterial infection, diabetes, cancer metastasis, etc. (no data). They are improved in bioavailability when administered orally, metabolic stability, liver or systemic clearance, or affinity for chemokine receptor CCR compared to prior art compds. and exhibit very low toxicity. Thus, 1-benzyl-4-piperidone, (2R,3R)-2-(tert-butoxycarbonylamino)-3-cyclohexyl-3-hydroxypropanoic acid, n-butylamine, and 2-(morpholin-4-yl)ethyl isocyanide were stirred in MeOH at 50° overnight to give, after workup, 1-benzyl-4-[2-(morpholin-4-yl)ethylaminocarbonyl]-4-[N-butyl-N-[(2R,3R)-2-amino-3-hydroxy-3-cyclohexylpropanoyl]amino]piperidine which was stirred in AcOH at 70° for 1 h to give, after workup, (3R)-1-butyl-2,5-dioxo-3-[(1R)-1-hydroxy-1-cyclohexylmethyl]-9-phenylmethyl-1,4,9-triazaspiro[5.5]undecane (II). A tablet and an ampule formulation containing specific compound I were described.

IT 461023-63-2P 676450-38-7P 676450-42-3P
676450-44-5P 676450-45-6P 676450-60-5P
676450-64-9P 676450-81-0P 676450-84-3P
676451-07-3P 676451-15-3P 676451-47-1P
676451-78-8P 676451-79-9P 676453-91-1P
676454-67-4P 676455-04-2P 676455-08-6P
676455-09-7P 676455-10-0P 676465-10-4P
676465-11-5P 676465-15-9P 676465-17-1P
676465-24-0P 676465-25-1P 676465-28-4P
676465-30-8P 676465-31-9P 676465-34-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of triazaspiro[5.5]undecane derivs. as chemokine receptor CCR5 antagonists and drugs)

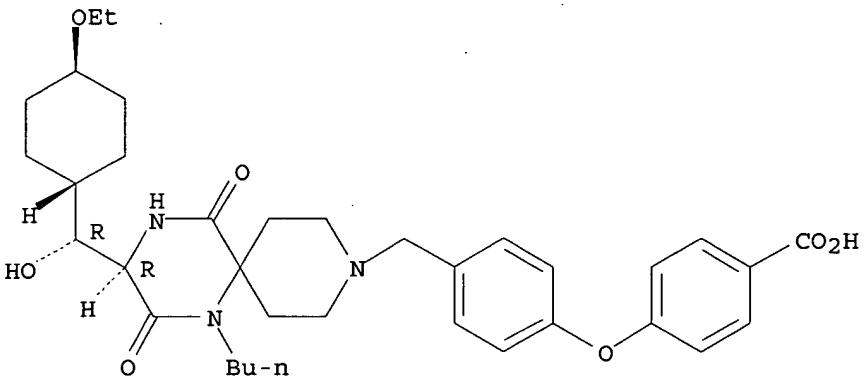
RN 461023-63-2 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



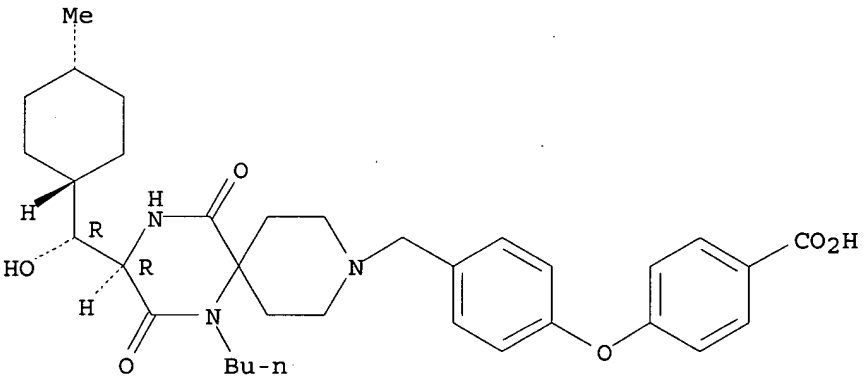
● HCl



● HCl

RN 676465-34-2 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-hydroxy(cis-4-methylcyclohexyl)methyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:252478 CAPLUS
DOCUMENT NUMBER: 140:264479
TITLE: G1-phase arresting compounds for inducing increased levels of β-chemokines
INVENTOR(S): Redfield, Robert R.; Amoroso, Anthony; Davis, Charles E.; Heredia, Alonsa
PATENT ASSIGNEE(S): University of Maryland Biotechnology, USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

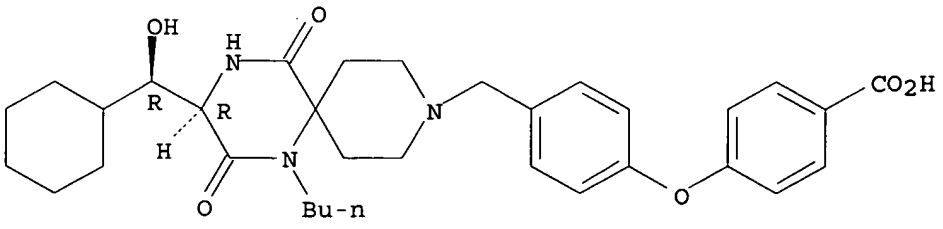
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024683	A2	20040325	WO 2003-US28697	20030912
WO 2004024683	A3	20040701		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2498934	AA	20040325	CA 2003-2498934	20030912
AU 2003266152	A1	20040430	AU 2003-266152	20030912
EP 1545539	A2	20050629	EP 2003-795698	20030912
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2006099170	A1	20060511	US 2005-527904	20050707
PRIORITY APPLN. INFO.:			US 2002-410714P P	20020913
			WO 2003-US28697 W	20030912

AB The present invention relates to methods for inducing increased levels and availability of β-chemokines by administering to a subject at least 1 G1-phase arresting compound, wherein the increased levels and availability of β-chemokines block chemokine/viral receptors thereby preventing or treating viral infections. The secretion of the β-chemokines by peripheral blood mononuclear cells in response to the activation started before lymphocytes entered the DNA synthesis phase of the cell cycle (S phase), reaches a peak by day 3 or 7 and then declined to low levels. The antivial activity is due the presence of the β-chemokines RANTES, and MIP proteins.

IT 461443-59-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(G1-phase arresting compds. for inducing increased levels of β-chemokines)

RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:252197 CAPLUS
DOCUMENT NUMBER: 140:281350
TITLE: Spiro compounds for inhibiting the first-pass effect
INVENTOR(S): Harris, James W.

10/527,193

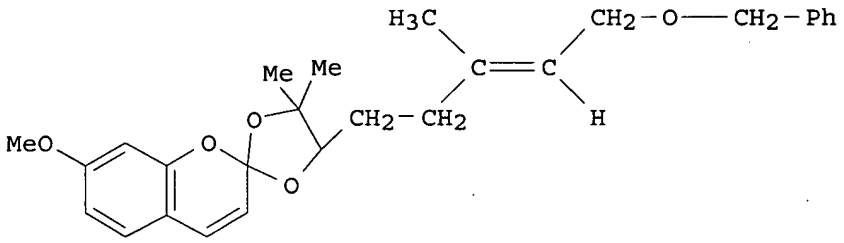
PATENT ASSIGNEE(S): Bioavailability System, LLC, USA
SOURCE: U.S. Pat. Appl. Publ., 133 pp., Cont.-in-part of U.S. Ser. No. 793,416.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004058982	A1	20040325	US 2003-422848	20030425
US 6248776	B1	20010619	US 1999-251467	19990217
US 6476066	B1	20021105	US 2001-793416	20010227
US 2005214366	A1	20050929	US 2005-81024	20050316

PRIORITY APPLN. INFO.:

US 1999-251467	A3	19990217
US 2001-793416	A2	20010227
US 1997-56382P	P	19970826
US 1997-997259	A2	19971223
US 2003-422848	B1	20030425

OTHER SOURCE(S): MARPAT 140:281350
GI



I

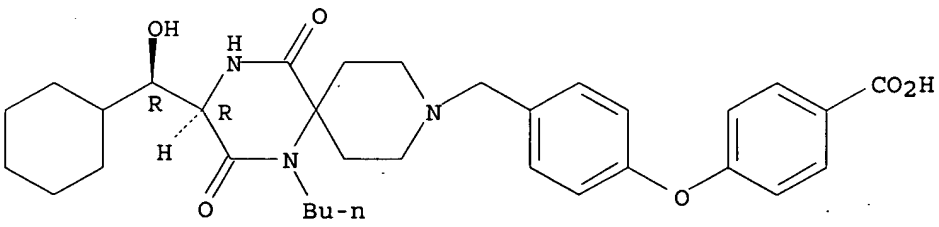
AB Compns., methods, etc. for addressing the first-pass effect are presented. An example compound prepared was I. Also processing citrus oils to obtain the compds. is given as examples as well as assessment of human cytochrome P 450-mediated biotransformation.

IT 461443-59-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(spiro compds. for inhibiting the first-pass effect)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

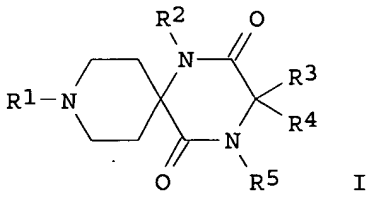


L4 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:334910 CAPLUS

DOCUMENT NUMBER: 138:331734
TITLE: Drugs comprising combination of triazaspiro[5.5]undecane derivative with cytochrome p450 isozyme 3a4 inhibitor and/or P-glycoprotein inhibitor
INVENTOR(S): Imawaka, Haruo; Shibayama, Shiro; Takaoka, Yoshikazu
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 183 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003035074	A1	20030501	WO 2002-JP2552		20020318
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2461545	AA	20030501	CA 2002-2461545		20020318
EP 1438962	A1	20040721	EP 2002-705299		20020318
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
CN 1571671	A	20050126	CN 2002-820391		20020318
BR 2002013372	A	20050201	BR 2002-13372		20020318
NO 2004001618	A	20040722	NO 2004-1618		20040421
ZA 2004003086	A	20050511	ZA 2004-3086		20040422
PRIORITY APPLN. INFO.:			JP 2001-324435	A	20011023
			WO 2002-JP2552	W	20020318

OTHER SOURCE(S): MARPAT 138:331734
GI



I

AB Drugs comprising a combination of triazaspiro[5.5]undecane derivs. represented by the following general formula (I): I wherein each symbol is as will be defined hereinafter; quaternary ammonium salts thereof, N-oxides of the same or nontoxic salts of the same with at least one cytochrome P 450 isoenzyme 3A4 inhibitor and/or at least one P-glycoprotein inhibitor. The drugs comprising such a combination, wherein the bioavailability of the compds. represented by the general formula I is elevated, are efficaciously usable as oral prepns. in treating various diseases.

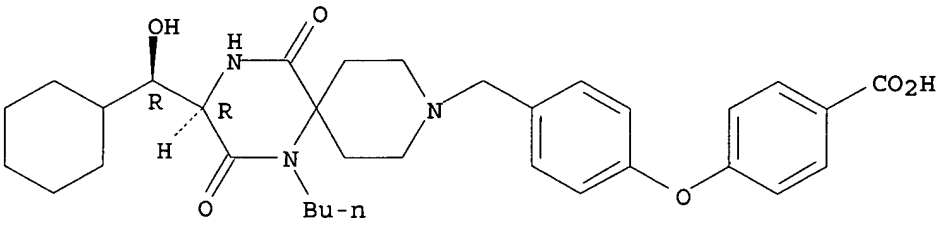
IT 461443-59-4

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drugs comprising combination of triazaspiro[5,5]undecane derivative with cytochrome P 450 isoenzyme 3a4 inhibitor and/or P-glycoprotein inhibitor)

RN 461443-59-4 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:736255 CAPLUS

DOCUMENT NUMBER: 137:263065

TITLE: Preparation of triazaspiro[5.5]undecane derivatives as active ingredients in remedies for inflammatory diseases

INVENTOR(S): Habashita, Hiromu; Hamano, Shinichi; Shibayama, Shiro; Takaoka, Yoshikazu

PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan

SOURCE: PCT Int. Appl., 379 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

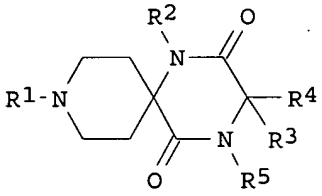
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002074770	A1	20020926	WO 2002-JP2554	20020318
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2440264	AA	20020926	CA 2002-2440264	20020318
EP 1378510	A1	20040107	EP 2002-705301	20020318
EP 1378510	B1	20060607		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002008167	A	20040309	BR 2002-8167	20020318
CN 1518551	A	20040804	CN 2002-810082	20020318
JP 3558079	B2	20040825	JP 2002-573779	20020318
NZ 528249	A	20050324	NZ 2002-528249	20020318
EP 1619194	A2	20060125	EP 2005-105154	20020318

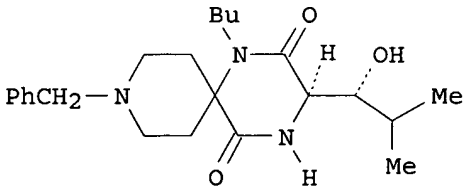
EP 1619194	A3	20060607			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR					
RU 2269528	C2	20060210	RU 2003-128067		20020318
AT 328884	E	20060615	AT 2002-705301		20020318
ZA 2003007167	A	20041101	ZA 2003-7167		20030912
NO 2003004148	A	20031114	NO 2003-4148		20030917
US 2004082584	A1	20040429	US 2003-472555		20030922
US 7053090	B2	20060530			
JP 2004196822	A2	20040715	JP 2004-66592		20040310
US 2005215557	A1	20050929	US 2005-135272		20050524
PRIORITY APPLN. INFO.:			JP 2001-79610	A	20010319
			JP 2001-160251	A	20010529
			EP 2002-705301	A3	20020318
			JP 2002-573779	A3	20020318
			WO 2002-JP2554	W	20020318
			US 2003-472555	A1	20030922

OTHER SOURCE(S): MARPAT 137:263065

GI



I



II

AB Title compds. [I; R1 = arylalkyl, nitrogen-containing-heterocyclylalkyl; R2 = alkyl, alkynyl; R3 = H, alkyl; R4 = H, alkyl; R3R4 = CHR; R = alkyl; R5 = H, alkyl], quaternary ammonium salts thereof, N-oxides thereof, nontoxic salts thereof, and drugs containing the same as the active ingredient are prepared Title compds. I, inhibiting the effects of chemokine/chemokine receptor, are useful in preventing and/or treating various inflammatory diseases, asthma, atopic dermatitis, urticaria, allergic diseases, nephritis, nephropathy, hepatitis, arthritis, rheumatoid arthritis, tumor metastasis control, etc. Thus, the title compound II was prepared from (2R,3R)-2-(tert-butoxycarbonylamino)-3-hydroxy-4-methylpentanoic acid, n-butylamine, N-benzyl-4-piperidone, and benzylisonitrile via intramol. cyclocondensation.

IT 461023-63-2P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

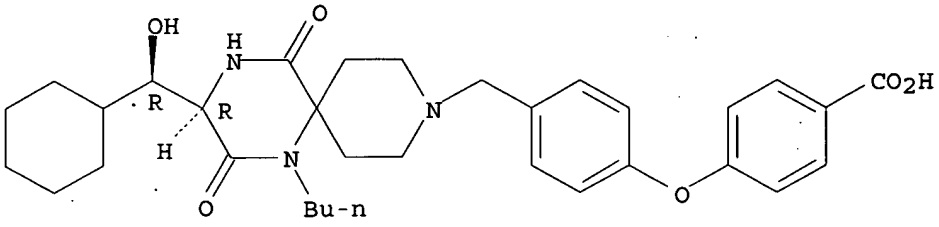
(preparation of triazaspiro[5.5]undecane derivs. as active ingredients in

remedies for inflammatory diseases)

RN 461023-63-2 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



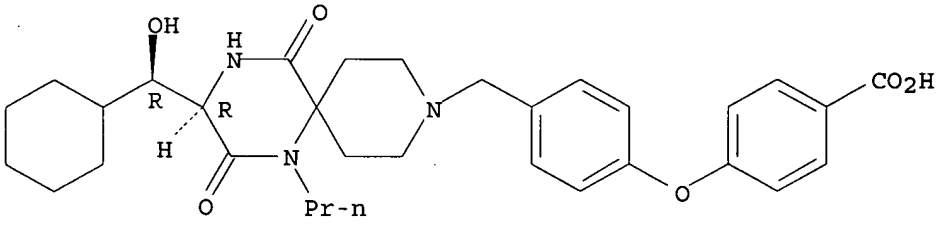
● HCl

IT 461024-08-8P 461024-49-7P 461443-59-4P
461444-02-0P 461444-36-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of triazaspiro[5.5]undecane derivs. as active ingredients in remedies for inflammatory diseases)

RN 461024-08-8 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1-propyl-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

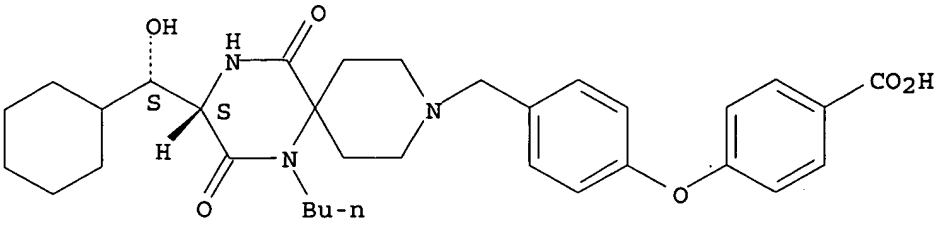


● HCl

RN 461024-49-7 CAPLUS

CN Benzoic acid, 4-[4-[[(3S)-1-butyl-3-[(S)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

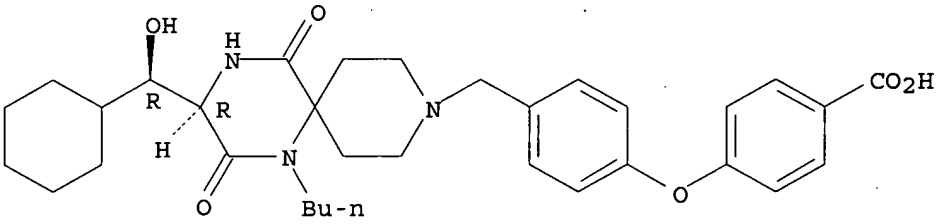
Absolute stereochemistry.



● HCl

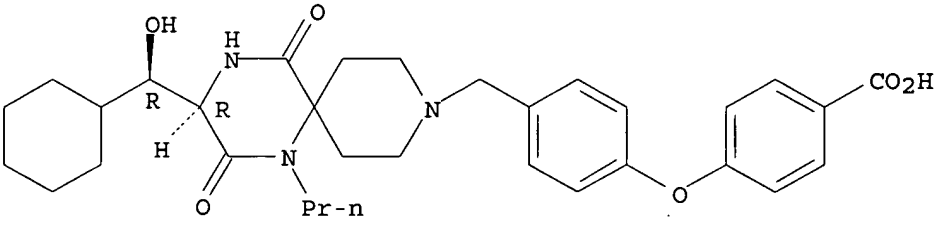
RN 461443-59-4 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



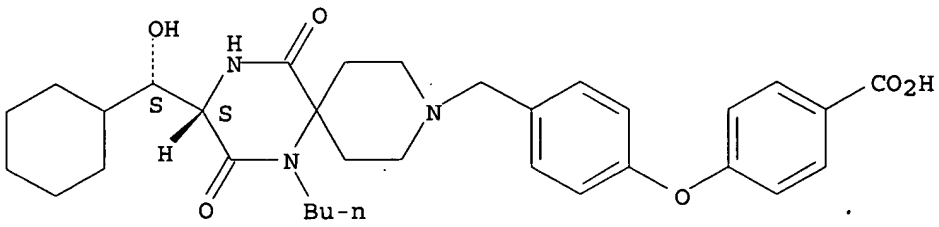
RN 461444-02-0 CAPLUS
CN Benzoic acid, 4-[4-[[(3R)-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1-propyl-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 461444-36-0 CAPLUS
CN Benzoic acid, 4-[4-[[(3S)-1-butyl-3-[(S)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 38 OF 38 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:736254 CAPLUS
DOCUMENT NUMBER: 137:263064
TITLE: Preparation of triazaspiro[5.5]undecane derivatives as the active ingredients useful in prevention or as remedy for HIV infection
INVENTOR(S): Mitsuya, Hiroaki; Maeda, Kenji; Shibayama, Shiro; Takaoka, Yoshikazu
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 680 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002074769	A1	20020926	WO 2002-JP2553	20020318
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2441162	AA	20020926	CA 2002-2441162	20020318
EP 1378509	A1	20040107	EP 2002-705300	20020318
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002008229	A	20040309	BR 2002-8229	20020318
CN 1533390	A	20040929	CN 2002-809833	20020318
NZ 528270	A	20051028	NZ 2002-528270	20020318
NO 2003004149	A	20031119	NO 2003-4149	20030917
ZA 2003007318	A	20040729	ZA 2003-7318	20030918
US 2004106619	A1	20040603	US 2003-472626	20030922
PRIORITY APPLN. INFO.:			JP 2001-79611 A	20010319
			WO 2002-JP2553 W	20020318

OTHER SOURCE(S): MARPAT 137:263064
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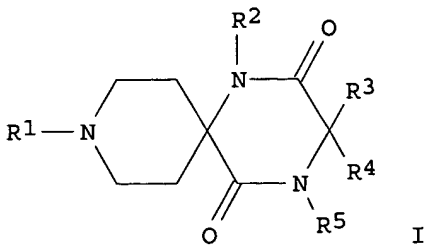

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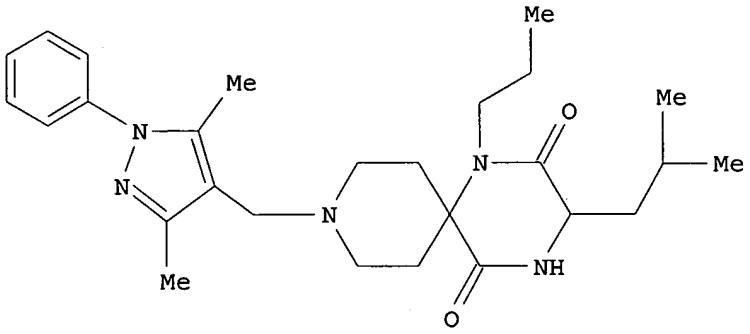


II

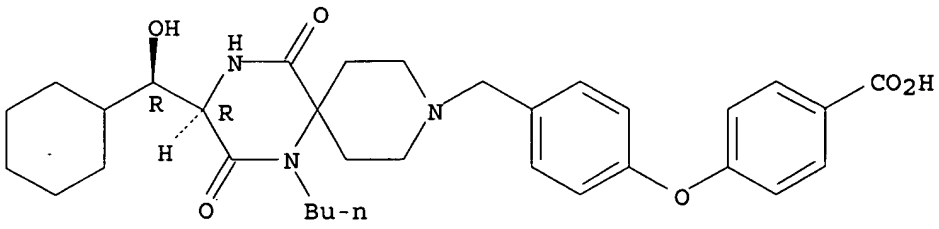
AB Title compds. [I; R1 = H, alkyl, alkenyl, alkynyl, COOH, SO2H, CONH2, CHO, heterocycle, aryl; R2 = alkyl, alkynyl; R3, R4 independently = H, alkyl, alkenyl, alkynyl, COOH, CONH2; R5 = H, alkyl, alkenyl, alkynyl], stereoisomers, quaternary ammonium salts thereof, N-oxides thereof and nontoxic salts of the same optionally combined with at least one preventive and/or remedy for HIV infection are prepared as preventives and/or remedies for HIV infection or preventives and/or remedies for AIDS caused by the infection. Thus, the title compound II·2HCl was prepared from N-(tert-butyloxycarbonyl)leucine, N-allyloxycarbonyl-4-piperidine, n-propylamine, and 3,5-dimethyl-1-phenyl-4-formyl-pyrazole via cyclization, on resin prepared from aminomethylated polystyrene hydrchloride.

IT 461023-63-2P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of triazaspiro[5.5]undecane derivs. as the active ingredients in prevention or remedy of HIV infection)

RN 461023-63-2 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-1-butyl-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



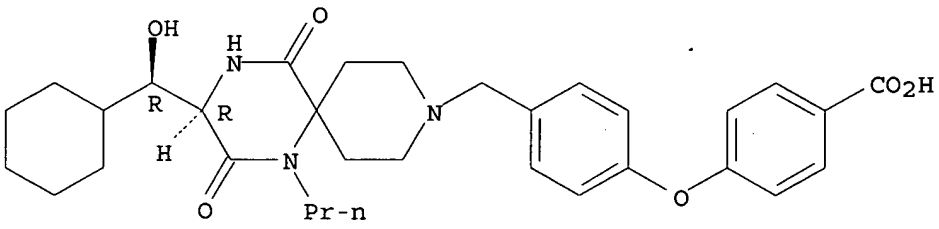
● HCl

IT 461024-08-8P 461024-49-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of triazaspiro[5.5]undecane derivs. as the active ingredients in prevention or remedy of HIV infection)

RN 461024-08-8 CAPLUS

CN Benzoic acid, 4-[4-[[(3R)-3-[(R)-cyclohexylhydroxymethyl]-2,5-dioxo-1-propyl-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

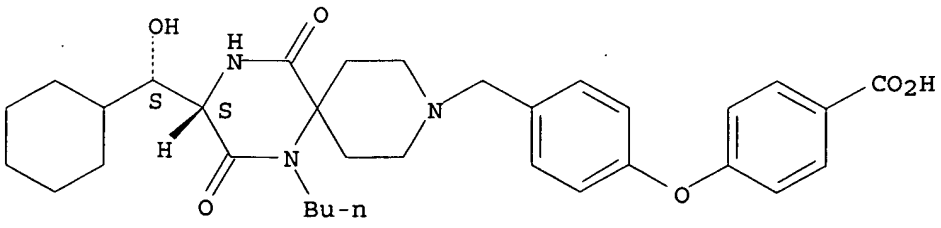


● HCl

RN 461024-49-7 CAPLUS

CN Benzoic acid, 4-[4-[[(3S)-1-butyl-3-[(S)-cyclohexylhydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl]methyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl